Tailoring treatment: a comprehensive review of precision medicine and biological therapies in inflammatory bowel disease

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Abstract.
Background: Inflammatory Bowel Disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), constitutes chronic immune-mediated disorders of the gastrointestinal tract. Their diverse inflammatory patterns and unpredictable course challenge effective diagnosis and treatment. With escalating global incidence, the evolving landscape of IBD management integrates precision medicine and a burgeoning array of biological therapies, aiming to revolutionize disease interception and personalized treatment strategies. Objectives: Examine the evolving role of precision medicine, genetic markers, biomarkers, and biological therapies in Inflammatory Bowel Disease (IBD)
management, assessing their impact on disease prediction, treatment response, and personalized care. Methods and Materials Required: The authors conducted a review as per the SANRA guidelines and searched for literature across PubMed and Google Scholar. RESULTS: Precision medicine and biomarkers redefine Inflammatory Bowel Disease (IBD) management. Genetic markers exhibit limited predictive power, necessitating integration with RNA sequences for refined disease trajectory understanding. Fecal calprotectin emerges as a transformative non-invasive tool for monitoring disease activity. Pharmacogenomics, exemplified by TPMT genotyping, showcases personalized treatment strategies. Anti-TNF-α therapies demonstrate superiority in inducing remission, yet newer agents like vedolizumab offer promising alternatives, especially in anti-TNF-α refractory patients. The evolving landscape of biological therapies signifies a shift towards targeted treatments, underscoring the need for nuanced patient-specific therapeutic approaches in IBD.

Keywords:
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INTRODUCTION

Inflammatory Bowel Disease (IBD) poses a considerable global health challenge, comprising Crohn's disease (CD) and ulcerative colitis (UC) as its primary manifestations. These chronic immune-mediated disorders of the gastrointestinal (GI) tract present varied inflammatory patterns, impacting different segments of the GI tract and featuring an unpredictable disease course. [36]

The diagnosis of IBD aligns with established guidelines integrating clinical practices and evidence-based recommendations, given the spectrum of symptoms ranging from mild discomfort to severe debilitation. Despite advancements, the complex nature of IBD extends beyond the GI tract, affecting multiple organ systems and profoundly influencing psychological, social, and economic dimensions. The escalating financial burden, estimated at billions of dollars annually in the United States alone, underscores the imperative for effective and targeted therapeutic strategies [37].

Diagnosing IBD follows established guidelines, incorporating international clinical practice tools and widely accepted evidence-based recommendations [38]. IBD can cause a spectrum of symptoms that can range from mild discomfort to severe debilitation. While Crohn’s commonly presents as inflammatory ileo-colonic involvement, and upper GI discomfort, with or without structuring or penetrating disease, ulcerative colitis usually involves the left-sided colon or presents as proctitis [39]. IBDs extend beyond the gastrointestinal (GI) tract, impacting virtually any organ system in the body, the most commonly affected being the musculoskeletal system [40]. Beyond the physical manifestations, the global impact of IBD extends to psychological, social, and economic dimensions. The estimated annual financial burden of IBD in the United States is around 30-40 billion dollars, as per the Crohn’s and Colitis Foundation of America (CCFA) [41].

IBD has become a global disease- Unlike Western countries, where IBD was considered rare just two decades ago, recent studies indicate a swift rise of IBD in Asia. While traditionally viewed as a disease primarily affecting the...
Western world, data from the past decade highlight a rising incidence in newly industrialized Asian countries like China and India [39,42,43].

Recent decades have seen that IBD treatment strategies now prioritize a 'treat-to-target' approach, aiming for both symptomatic relief and specific outcomes. In CD, the focus is on alleviating abdominal pain and normalizing stool frequency, while also healing endoscopic ulcerations. For UC, targets include resolving rectal bleeding, addressing altered bowel habits, and achieving endoscopic remission [44].

Without a definitive cure, immunosuppressants are the mainstay of medical management for IBD. However, notable advances in recent decades have reshaped IBD’s medical therapy.

It all started with a groundbreaking randomized controlled trial (RCT) of IBD therapeutics, led by Truelove and Witts in 1955, which brought in corticosteroids as induction therapy for UC during the era when surgical and supportive care were the primary options [45]. Over the subsequent 50 years, conventional treatments, including corticosteroids, aminosalicylates, and immunosuppressants (such as thiopurines, methotrexate, tacrolimus, and cyclosporine), constituted the core of medical care for IBD before the advent of biologics [46]. The first biologic, introduced over two decades ago, was the tissue necrosis alpha (TNFα) inhibitor Infliximab, followed by several others with similar or different mechanisms of action like Adalizumab, Certolizumab amongst others [47, 48]. Most of the biologics are now nearing patent expiry, ushering in biosimilars or the ‘follow-on biologicals’, which are emerging as noteworthy to alleviate the economic burden associated with chronic conditions like IBD [49]. Moreover, insights drawn from lessons learned in the pre-biological era have rekindled the interest in developing oral small-molecule-based therapies [46] Several distinctions between monoclonal antibodies and small molecule drugs (SMDs) have been noted, favoring SMDs. Despite the revolutionary nature of biologics, it's interesting to note that about one-third of patients are primary non-responders to induction therapy with current biologics, and a substantial proportion of initially
responsive patients lose response over time [50].

All in all, in this comprehensive review, we embark on an exploration of precision medicine and biological therapies as promising avenues for tailoring treatments in IBD. By scrutinizing the current treatment landscape, identifying challenges, and examining the rationale for personalized approaches, we aim to provide insights that may revolutionize the care and outcomes for individuals with IBD.

**Precision Medicine in Inflammatory Bowel Disease**

The incidence and prevalence of IBD are increasing day by day, although its pathogenesis remains unclear as it is relapsing and remitting [2, 9]. However, etiological factors concentrate on the genome, exposome, microbiome, and immunome [2, 10].

It is slowly becoming clear that initial therapy plays the most important role in IBD treatment [2]. Thus it becomes more important to identify the disease as early as possible and target the primary processes that actually cause the disease or transmit it to a clinical stage [6, 10].

Patients are prescribed corticosteroids and sometimes surgery is also needed as the disease is not recognized in its early phase leading to a lot of complications [5].

Therefore predicting the response, relapse, side effects, and cost-effectiveness is required to allow the patients to get the right drug in its right dose at the right time [2].

Hence there is a need for precision medicine which provides a multicentric approach so that research and data from different fields are integrated together to enable the treatment and detection of disease [1, 2].

However, some gaps in precision medicine should be addressed to have a reliable patient approach. Some of these are understanding and predicting the natural history of IBD: disease susceptibility, activity, and behavior; predicting disease course and treatment response, and optimizing current and developing new molecular technologies [8].

**Genetic testing**

Predicting the course of IBD is important for optimizing treatments. Since genetic factors remain stable over time, are present long before disease onset, and are not open to subjective interpretation, they are promising for disease
prediction. However, only a few associations between genetic variants and IBD phenotypes have been reported [1].

Genetic-wide association studies have recognized various gene loci (almost 240 or more) and some of the processes such as epithelial barrier dysfunction, antimicrobial defense disruption, immune dysregulation, etc. may be involved in causing the disease.[1, 2, 4, 6, 10].

The molecular architecture of this disease course has been defined through genetics at a methylome, glycome, and proteome level [2, 7]. The RISK study group shows that integrating genetic-wide studies with RNA sequences and transcriptional risk scores can help predict the disease and its course [9].

Another study suggests that IBD has a polygenic nature which will be better predicted by polygenic risk scores, rather than by a single allelic odds ratio [OR] for a rare monogenic mutation. The strongest risk of IBD occurs in NOD2 variants [1, 9, 10]. Apart from the polygenic nature some cases also show monogenic IBD (over 50 single genes have been identified) and patients show rare genetic disorders and early onset IBD [1, 3, 4].

There has been increasing evidence of IBD in family members showing a history. Studies of familial risk in IBD have reported a 4–15 times greater risk for IBD in first-degree relatives. Ongoing cohorts such as the GEM study, the Multiplex Orthodox Jewish Family at Mount Sinai, the PREDICTS study, the UK Twin study, the EPIC cohort, the Dutch TWIN-IBD study, the Swedish IBD Twin Study provide evidence to gain insights into preclinical disease period and possible prevention strategies[1, 10].

Because of its complex genetic nature, the genotype is not fully predictive of the phenotype.

Genetic markers will thus not be able to entirely predict the natural course of the disease or the clinical outcome and hence the need to look out for transcriptional and other serological markers is also important. Not only genetics but it is also important to highlight the effect of demographic, environmental, lifestyle, and clinical risk factors [1, 2, 9, 10].

Biomarkers

A biomarker objectively measures normal biological
processes, pathogenic processes, or responses to an exposure or intervention. It can be derived from molecular, histologic, radiographic, or physiologic characteristics. Biomarkers are categorized into diagnostic, monitoring, response, predictive, prognostic, and safety types [11]. They play a crucial role in various aspects of IBD management, from facilitating accurate diagnosis to optimizing therapeutic efficacy and predicting disease outcomes while being cost-effective and easy to use.

ASCA and ANCA are the pioneering markers of IBD, having been utilized for decades to differentiate between UC and CD [12, 13]. While erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and Lactoferrin are commonly used biomarkers, their non-specific nature limits their diagnostic utility [14, 15, 16].

These inflammatory markers can be elevated in various pathologies, encompassing infections, autoimmune diseases, and even malignancies. Fecal calprotectin is extensively used in IBD, offering a non-invasive way to detect inflammation, differentiate IBD from IBS, and monitor disease activity and treatment response [17, 18, 19, 20].

A diverse arsenal of newer agents like anti-OmpC (anti-outer-membrane porin C), anti-flagellin (CBir-1, A4-Fla2 & FlaX) antibodies, SAA (serum amyloid A), OSM (Oncostatin M), PGE-MUM (Prostaglandin E-major urinary metabolite), microRNA is empowering clinicians to navigate the intricate landscape of IBD with greater precision [21, 22, 23].

Beyond these, CABP (Crohn's disease (CD) antibody binding polypeptide), ECP (Fecal eosinophil cationic protein), and EDN (eosinophil-derived neurotoxin), SPP24 (secreted phosphoprotein 24) and numerous other novel candidates are being explored [24, 25, 26].

With the recent advances in metagenomic technology, each patient’s unique gut microbiome is being evaluated to further understand the pathogenesis and to assess the clinical progression and treatment response in IBD. The realm of biomarker discovery is expanding, with researchers now delving into the potential of sweat, saliva, and urine for non-invasive markers. By combining data from various sources such as serum biomarkers, histological features, and clinical
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assessment, clinicians can now provide a more personalized treatment approach [12, 27, 28, 29, 30].

**Pharmacogenomics**

Pharmacogenomics is the study of how genetic variations influence drug response. Its ultimate objective is to craft a personalized pharmacogenetic roadmap for each patient, paving the way for the safest and most effective treatment journey. This hinges on unraveling how genetic polymorphisms in drug targets, metabolizers, and immune regulators sculpt both drug response and adverse effects. For example, in the case of thiopurine treatment, variants in the thiopurine S-methyltransferase (TPMT) gene can lead to excessive drug accumulation and toxicity. Hence, the FDA recommends TPMT genotyping before initiating thiopurine therapy in IBD.

Paralleling the NOD2 gene's influence on anti-TNF response, MTHFR variants dictate methotrexate efficacy and side effects, while the NAT2 gene modulates 5-ASA therapy; thus showcasing pharmacogenomics' growing power to individualize IBD treatment [31,32, 33]. Similarly, elevated MDR (multi-drug resistance) gene expression in lymphocytes and intestinal cells, seen in patients with poor response to glucocorticoids, suggests this could be a novel biomarker for resistance and a target for therapeutic interventions [34]. Even though numerous pharmacogenomic associations have been discovered for conventional treatments, there needs to be more of this information in the case of monoclonal antibodies, hence TDM (therapeutic drug monitoring) is recommended [35].

Extensive collaborative studies to solidify these findings and a multi-pronged approach that combines all the above tools are crucial to unlocking true personalized care in IBD patients.

**Biological Therapies in Inflammatory Bowel Disease**

**Anti-TNF-α Therapy**

One of the breakthrough observations over the past two decades was the identification of the critical role of tumor necrosis factor-alpha (TNF-α) in the pathogenesis of chronic gut inflammation in CD. TNF-α is elevated in the stool, mucosa, and blood of patients with IBD. Biological therapies are superior to placebo in inducing remission of active CD and UC, and in preventing relapse of quiescent CD [51].
Four of the anti-TNF-α antibodies are widely used in the treatment of IBD: infliximab, adalimumab, golimumab, and certolizumab pegol. Infliximab is a recombinant chimeric IgG1 mAb. It was the first monoclonal antibody approved for treating patients with IBD. Infliximab induces clinical remission and mucosal healing in patients with IBD who are unresponsive to non-biologic treatment. The half-life of this antibody is approximately eight to ten days. Adalimumab is a fully human recombinant IgG1 mAb with a longer half-life than infliximab, approximately 10-13 days, it requires less frequent administration, which is subcutaneous [52, 53, 54].

Golimumab is a recombinant, completely humanized IgG1 mAb. It is beneficial for patients after the failure of infliximab and adalimumab therapy and has a half-life of seven to twenty days. It is safe and maintains its efficacy after two years of maintenance therapy [55].

Certolizumab pegol is a modified human mAb. Its half-life is two weeks and it is administered subcutaneously. Results from some studies showed clinical benefits in patients refractory to other biological therapies. The PRECISE 2 trial proved that certolizumab pegol (400 mg) was safe and effective in treating moderate-to-severe CD over 26 weeks. In patients with ease duration <1 year, the response rate at 26 weeks was 89.5%, whereas in patients with CD for ≥5 years, it was 57.3%. Patients who started certolizumab pegol treatment early in their disease showed significantly higher response rates than those who started treatment later. A recent pooled analysis of 4 clinical trial programs (EXTEND, UNITY, VERSIFY, CPT-13 BIOSIMILAR) was presented at the ECCO Congress 2022 and confirmed that infliximab achieved a higher proportion of 1-year endoscopic healing compared to adalimumab, ustekinumab, and vedolizumab in CD patients, but not in bio-naive patients [56].

According to the Swiss IBD cohort study, when immunosuppressive therapy is started in the early stages of the disease, it may be possible to lessen structural bowel damage using immunomodulators or TNF antagonists. Anti-Interleukin Therapy Ustekinumab is a fully humanized IgG1k mAb. It shows clinical efficacy in moderate to severe CD. In most CD patients, remission is maintained after three years.
There is some evidence to suggest that people with shorter disease duration may benefit more from ustekinumab. Furthermore, the effectiveness of ustekinumab has also been demonstrated in UC. This drug is now approved for both types of IBD [56, 57].

The SEAVUE study compared ustekinumab with adalimumab in 386 bio-naive patients with moderate to severe CD over 52 weeks. This study showed similar efficacy between the 2 groups 65% in the ustekinumab group vs. 61% in the adalimumab. Interestingly, the rapidity of response was also similar between the two groups. The most recent meta-analysis in CD which included ustekinumab concluded that infliximab or adalimumab are the best first-line agents, and ustekinumab is a preferred second-line agent in patients with prior anti-TNF alpha exposure[58].

**Anti-Integrin Therapy**

These drugs are important for those IBD patients who do not respond to an anti-TNF-α treatment. Natalizumab is a recombinant humanized IgG4. This drug stops the migration of inflammatory cells across the cell layers and must be administered for a long time to achieve positive results. Natalizumab is associated with an increased risk of progressive multifocal leukoencephalopathy (PML) caused by the reactivation of the latent human JC polyomavirus. This adverse reaction profile has resulted in FDA approval with additional stipulations, mandating its long-term use as monotherapy with no concomitant immunosuppressive agents, in the hope of preventing PML. [9]

Vedolizumab is a humanized mAb. FDA and European Medicine Agency (EMA) approved vedolizumab for treating moderate to severe UC and CD patients who did not respond to the anti-TNF-α treatment. However, its efficacy may be greater in IBD patients naive to anti-TNF-α therapy. Importantly, it does not cause strong immunosuppressive systemic effects since it acts selectively in the intestine. However, due to its high selectivity, vedolizumab is not effective in reducing extra-intestinal symptoms. The VARSITY trial, conducted over 1 year, compared 383 UC patients treated with vedolizumab to 386 UC patients treated with adalimumab [59].

At week 52, the clinical remission rate (31.3% vs. 22.5%)
and endoscopic improvement (39.7% vs. 27.7%) were significantly higher with vedolizumab compared to adalimumab. There were no striking safety differences between the two drugs over the 1 year. A real-world observational cohort of patients treated with vedolizumab showed that a CD illness duration of less than two years was substantially linked to greater rates of endoscopic healing and steroid-free clinical remission at six months.

RESULTS

The evolving landscape of Inflammatory Bowel Disease (IBD) management is marked by significant strides in precision medicine and the expanding arsenal of biological therapies. Precision medicine, drawing from genomics, exposomics, microbiomics, and immunomics, offers promise in the early interception of IBD. Genetic markers, though numerous, exhibit limited predictive power due to the intricate polygenic nature of the disease.

Integration of RNA sequences and transcriptional risk scores shows potential in refining predictive models, offering a more nuanced understanding of disease progression. Biomarkers have reshaped the diagnostic and prognostic landscape of IBD. Fecal calprotectin emerges as a transformative tool for non-invasive monitoring of disease activity and treatment response, revolutionizing clinical assessment. Pharmacogenomics, decoding genetic variations' influence on drug response, showcases personalized treatment strategies, exemplified by mandatory TPMT genotyping before thiopurine therapy initiation. The advent of biological therapies, particularly anti-TNF-α agents, marks a significant milestone in IBD treatment.

These agents demonstrate superiority in inducing remission and mucosal healing. However, the emergence of newer agents like vedolizumab, with its gut-selective action, presents a promising alternative, especially in anti-TNF-α refractory patients. Nonetheless, their selective effectiveness emphasizes the necessity for a nuanced understanding of patient-specific responses to different therapies.

DISCUSSIONS

The landscape of IBD treatment is on the brink of a
paradigm shift, fueled by advancements in precision medicine and biological therapies. Precision medicine offers hope in early disease interception, yet the predictive power of genetic markers remains a challenge due to the complex nature of IBD.

Biomarkers, particularly fecal calprotectin, redefine disease monitoring, enhancing clinical assessment. Pharmacogenomics exemplifies personalized treatment strategies, reshaping therapeutic interventions, and optimizing drug efficacy. Biological therapies, notably anti-TNF-α agents, have revolutionized IBD treatment.

However, the emergence of newer agents like vedolizumab signifies a shift toward more targeted therapies, albeit with varying effectiveness. Integration of genetic insights, biomarker discoveries, and pharmacogenomic applications holds promise in tailoring personalized care. Yet, collaborative efforts and a multifaceted approach are imperative to harness the full potential of tailored treatments and significantly improve outcomes for individuals battling IBD.

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