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Conditioning Regimens of B Cell Immunodeficiencies Current Perspectives and Future Strategies

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Abstract

As primary immunodeficiencies (PI) have evolved rapidly over the past 20 years, and immune dysregulation has been recognized as a characteristic in some, the term "inborn errors of immunity" (IEI) has become a more comprehensive description of these conditions. Monogenic disorders of the immune system have historically been characterized as disorders affecting T cells, B cells, or a combination of T and B cells. Innate immune disorders can also be classified as a monogenic disorder. Recently, immunologists have also recognized that some genes are incompletely penetrant or express themselves differently across genotypes and result in IEI due to incomplete penetrance or variable expression. In the IUIS classification of immune deficiencies, small molecule inhibitors and biologics are used to treat a subset of disorders called immune dysregulation. Until recently, the only treatment options were prompt treatment of infections, gamma globulin replacement, and bone marrow transplant. Small molecule inhibitors, biologics, gene therapy, and adoptive transfer of virus-specific T cells are all available to fight viral infections in immunocompromised patients. Over the past two decades, several significant contributions have fuelled rapid advancements in clinical immunology. As a result of educational efforts to recruit young immunologists into the field, a world-wide community of clinicians and researchers interested in rare diseases has grown. In addition, IEI's efforts to raise global awareness have contributed to international collaborations, as have advances in diagnostic genetic testing, newborn screening, molecular biology, gene correction, immune modulators, and the ex vivo expansion of engineered T cells. The purpose of this short communication is to provide a brief compendium of IEI that affect B cells at specific stages of their development, as well as some educated viewpoints on how these disorders may be managed in the future.

Keywords: B cells, Immunodeficiency, Humoral immunity

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Introduction

Both extracellular and intracellular pathogens are protected by the anamnestic immune response. In order to eliminate invading pathogens and generate sterilizing immunity, two distinct subsets of cells, the B cells (which target extracellular pathogens) and the T cells (which eliminate intracellular pathogens), play complementary roles. B cell receptors (BCRs) and immunoglobulins (Igs) play a significant role in B cell-associated immune responses. The understanding of how the Ig molecule interacts with its cognate antigen and triggers the B cell response has led to revolutions in two major domains of modern healthcare: laboratory diagnostics and immunotherapy. Without Kohler and Milstein discovering the process to generate monoclonal antibodies (MAb) in the early to mid-1970s, laboratory medicine would have been in a state of arrested development. A number of disease-specific biologics have also been developed since this seminal discovery in the subsequent decades. A number of key molecular regulators of B cell development and responses have been identified from studying inborn errors of B cell immunity [1]. Humans were first diagnosed with X-linked Agammaglobulinemia (XLA) as an inborn error of immunity (IEI). Based on an analysis of clinical presentations and laboratory findings in patients with predominantly B cell IEI, this review highlights how our understanding of B cell development and humoral immunity has evolved over the past 70 years [2]. The report begins with a brief history of XLA, one of the prototypical B cells IEIs, followed by an overview of what we currently know about a few representative B cell IEIs that are routinely considered as part of the differential diagnosis in patients with deficiencies in B cells and antibodies. Following our discussion of diagnosis and treatment options for B cell IEI, we finish by offering some thoughts on how the future may affect the way we diagnose and treat B cell IEI [3].

A Look Back at the Past

Novel therapeutics have been developed and applied as a result of advances in understanding immune mechanisms of rheumatologic diseases. A number of small molecule inhibitors, fusion proteins, and biologics are now being "borrowed" from other indications and used to treat autoimmunity, lymphoproliferation, and malignancy involving IEI. Therapeutic agents are used in precision medicine to modulate intracellular pathways whose function is altered by genetic defects [4]. Some IEIs are being treated using this approach. It is inherently difficult for rare diseases like IEI to be studied in well-controlled clinical trials and these new therapeutics must be applied in unique ways by clinical immunologists to improve patient outcomes [5].

Humans are the first species to be identified with the IEI XLA. The laboratory examination of a serum sample taken from an eight-year-old boy with multiple episodes of bacterial sepsis in early childhood

revealed that no globulin fraction was present when the sample was electrophoresed. The exact molecular defect contributing to agammaglobulinemia was not identified for forty years after this seminal observation. Bruton's tyrosine kinase (BTK) is a cytoplasmic tyrosine kinase encoded by a gene on the long arm of the X-chromosome. Approximately 1 in 200,000 children suffer from this disorder [6]. It is typically diagnosed as maternal antibodies start to decline, resulting in an absence of an endogenous humoral immune response, which makes children susceptible to childhood infectious diseases. As a result of hematopoietic progenitor stem cells, BTK is found in several cell types, but what separates B cells from the other BTK-containing cell lineages is the way that signals transduced by this molecule are crucial to the generation of naive, mature B cells in the bone marrow, which enter the circulation. It should be noted, however, that BTK expression is not required in terminally differentiated B cells, since plasma cells do not express it [2, 7]. Consequently, developing B cells in the bone marrow fail to differentiate past pre-B-I state if there is no BTK expression or if its function is subverted by a crippling mutation. Consequently, the patient is rendered agammaglobulinemic because the circulating lymphocyte pool lacks B cells. As a result, other hematopoietic cells such as monocytes continue to mature uninterrupted when BTK is not expressed or functioning. Despite the fact that the effector functions of these cells are usually compromised as a consequence of this defect, these cells can successfully egress out of the bone marrow and seed the circulatory compartment. By assessing the presence or absence of BTK expression in monocytes by flow cytometry, we exploit this dichotomy in the requirement of BTK relating to the maturation of B cells and monocytes in the diagnostic lab. In agammaglobulinemic patients, inadequate BTK expression can be quickly ruled out as a potential contributor to agammaglobulinemic symptoms. Monocytes that have had the X chromosome randomly inactivated (lyonized) can also be rapidly identified as XLA carriers using flow cytometry. However, since mutated BTK gene-expressing B cells are not able to egress from the bone marrow, the wild-type BTK gene always is expressed in circulating B cells of XLA carriers [2, 8].

It is necessary to assess the expression of BTK by flow cytometry in order to diagnose XLA clinically. In the histogram overlay plots, you can see whether the indicated cellular subsets express BTK protein in the cytosol. In order to identify circulating T cells, B cells, and monocytes, MAb targeting CD3, CD19, and CD64 were used. A monoclonal antibody specific for BTK (BD Biosciences, San Jose, CA, USA) was used to detect cytosolic BTK (blue histogram) after fixation, permeabilization, and staining. In parentheses, the number represents the clinically validated reference range (5^{th} - 95^{th} percentiles) for that particular cell subset derived from background-subtracted median fluorescence intensity of BTK expression. In each histogram overlay plot, the numbers indicate the background-subtracted MFI of BTK expression for each donor cell subset. A histogram overlay plot for carriers' monocytes shows the background-subtracted BTK MFI values, the frequency of BTK+ and BTK+ monocytic populations, and the background subtracted BTK MFI values [9, 10]. To determine the specificity of the BTK signal, a dose-matched, isotype control Ab (pink histogram) was used. Due to their lack of BTK expression, T cells serve as another internal specificity control system.

An assessment of BTK expression using flow cytometry to assist in the diagnosis of XLA. Using histogram overlay plots, the indicated cellular subsets can be identified based on the presence or absence of BTK protein expression in their cytosols. Lineage-directed MAb targeting CD3, CD19, and CD64 expression on the surface of circulating T cells, B cells, and monocytes were used to identify circulating T cells, B cells, and monocytes [11, 12]. BD Biosciences of San Jose, Calif., USA, provided clone 53/BTK, a monoclonal antibody specific for BTK (blue histograms) which was used to detect cytosolic BTK (blue histograms). Those numbers in parentheses indicate the reference ranges (5^{th} - 95^{th} percentiles) for that particular cell subset, derived from background-subtracted median fluorescence intensities (MFIs) of BTK expression. Within each histogram overlay plot, the numbers reflect background-subtracted BTK expression in the specific cell subset for each donor [13]. Detailed histogram overlay plots are shown for the carrier monocytes, showing the background-subtracted BTK MFI values as well as the frequency (%) of BTK(+) and BTK(−) monocytic populations. Additionally, a dose-matched, isotype control Ab (pink histograms) was used to test the specificity of the BTK signal. A second internal control of specificity is provided by T cells, since they lack BTK expression [14].

In the Present Day

Molecular diagnosis is becoming clearer for patients who previously had an unclear molecular diagnosis as primary B cell IEI rapidly expands. The predominantly B cell IEI umbrella includes nearly 50 distinct clinical entities [15].

Detailed discussion of each clinical entity is beyond the scope of this report; nevertheless, some of the disorders have been highlighted, including a few recently discovered (PU.1, and Ikaros transcription factor disorders), which are important in the development and differentiation of B cells despite being uncommon [16].

IEI predominantly associated with B cells. According to both the 2019 update from the international union of immunological societies (IUIS) and the 2022 update, this figure lists both genetic defects underlying the disease as well as its name (in red). In addition to the phenotype of the disease as well as the degree to which the different isotypes of Ig as well as the number of B cells are decreased, these defects can display both autosomal recessive as well as autosomal dominant patterns. Since heterozygous variants of this gene can also occur in healthy individuals, the variants can be considered disease-modifying rather than disease-causing. Transcription factor: TF [17].

B cell maturation and differentiation genes that target defined steps. A description of the immune defects caused by the genes (labelled in red) is presented in this report. Despite not being included in the latest IUIS classification for primarily Ab deficiencies, these genes are associated with defects in Ab isotype switching (CD40LG) and immune dysregulation. In addition to early onset hypogammaglobulinemia (CTLA4 and LRBA), which is part of a spectrum of widespread immune aberrations that also include autoimmunity, these genes contribute to immune dysregulation. Bone marrow is home to these cell populations [18].

PU.1

The most common congenital agammaglobulinemia is XLA, but several other congenital agammaglobulinemias can be inherited either autosomal dominantly or recessively (μ chain, Igα, Igβ, λ5, E47, BLNK, PIK3R1). Congenital agammaglobulinemia has recently been linked to PU.1 haploinsufficiency. A patient suffering from PU.1-related agammaglobulinemia presents to the hospital within the first year of life. They usually suffer from recurrent sinopulmonary infections and invasive bacterial infections. These patients do not appear to have mycobacterial infections despite a quantitative and qualitative conventional dendritic cell deficiency. As an example of an early-stage defect, PU.1-related B cell immunodeficiency results in the arrest of the pro-B cell stage.

Disorders of the Ikaros family of transcription factors (IKZF1, IKZF2, Helios, and IKZF3)

IKZF1

There are several members of the Ikaros protein family, including IKZF1 (Ikaros Zinc Finger 1), IKZF2 (Ikaros Zinc Finger 2-Helios), and IKZF3 (Ikaros Zinc Finger 3-Aiolos). These protein families regulate lymphocyte development by binding to DNA through zinc fingers. It is caused by mutations in IKZF1 in the latter stages of B cell development that lead to an IEI that affects B cells. The development of high-risk B-cell acute lymphoblastic leukaemia (B-ALL) has been associated with somatic IKZF1 pathogenic variants, but we have now expanded our understanding of the IKZF1-linked spectrum of diseases to include several IEIs resulting from germline IKZF1 variants. Even though these genetic defects are incompletely penetrant, the clinical phenotype in symptomatic patients includes an increased susceptibility to bacterial infections and less frequently, viral infections, as well as autoimmunity, immune dysregulation, and possibly malignancy (B-ALL). Pneumocystis pneumonia and T-cell ALL are more common in dominant-negative variants. Contrary to this, haploinsufficiency-associated variants located at the N-terminus result in a common variable immunodeficiency (CVID)-like phenotype, while variants affecting the C-terminus impair Ikaros dimerization and cause hematologic disorders, including cytopenia's and tumors. It has been reported that eight individuals with inflammatory, allergic, and autoimmune manifestations with aberrant T-cell differentiation were characterized by reduced numbers of regulatory T cells, increased numbers of Th2 cells, peripheral eosinophilia, and abnormal plasma cells, all of which were caused by a gain-of-function variant in the DNA-binding domain [2].

IKZF2, Helios, and IKZF3

CD8 T cells are highly expressed with IKZF2 pathogenic variants; therefore, individuals with IKZF2 pathogenic variants may present with immune dysregulation or autoimmune phenotypes or some combination of these. In addition to hypogammaglobulinemia, chronic lymphadenopathy, immune thrombocytopenia, and thrush, the clinical presentation can include systemic lupus erythematosus. Two families with mutations in IKZF3 show impairments in B cell maturation, compared to IKZF2-related defects. One family with a heterozygous missense variant in IKZF3 developed increased susceptibility to Epstein-barr virus (EBV), sinopulmonary infections, and abnormal T cell development with increased memory and activated T cell subsets. An additional family with a combined B and T cell deficiency phenotype, Pneumocystis jiroveci pneumonia, and chronic lymphocytic leukaemia had a heterozygous variant as well [7].

Hyper IgM syndromes

The hyper IgM syndromes (HIGM) are a group of IEI that affect B cell development. Approximately 65 - 70% of all hyper IgM cases are caused by X-linked defects in CD40 ligand (CD40L). A hyper IgM phenotype is characterized by elevated IgM concentrations and low levels of serum IgG, IgA, or IgE. The CD40 ligand gene (CD40LG) mutations resulting in HIGM were identified in 1992. It is also known as immunoglobulin class-switch recombination (Ig-CSR). In these diseases, the inability of mature B cells to switch isotypes is the principal underlying defect. CD40, activation-induced cytidine deaminase (AID) and uracil-DNA glycosylase (UNG) deficiency disorders are briefly discussed in this report, although more genes have been identified in non-X-linked HIGM syndromes [12].

CD40L (and CD40) deficiency

Defects in CD40L and CD40 cause both humoral and cellular immunodeficiency, since CD40L and CD40 interact to co-stimulate T cells. There are many clinical similarities between CD40 and CD40L deficiencies, including susceptibility to pathogens.

AID

Recombination between classes and somatic hypermutation are mediated by AID (encoded by AICDA). When patients with AID deficiency develop symptoms, they usually do so in their first decade of life, but they can also present in their second or third decade of life. There have been reports of other pathogens as well as encapsulated bacteria infecting these patients. AID deficiency is associated with non-infectious complications such as lymphoid hyperplasia and autoimmunity.

UNG

As well as class-switch recombination, UNG plays a key role in somatic hypermutation. In addition to AID-induced deamination, it is also important for its enzymatic activity. Although UNG deficiency is rarer than AID, the clinical phenotype is the same [2].

CVID and CVID-like disorders

In the development and differentiation of B cells beyond the class-switching phase, CVID is the most common defect. CVID was first described clinically in 1954 in an adult female with agammaglobulinemia, recurrent infections, including bacterial pneumonia, as well as chronic lung disease and diarrhoea. Traditionally, CVID has been perceived as a disorder associated with recurrent and prolonged infections and hypogammaglobulinemia in adults. According to U.S. and European registries, 18 - 42% of CVID cases are pediatric. Approximately two to four people per 100,000 are believed to suffer from CVID, and there is no clear preference for any particular ethnicity or gender. Upon diagnosis, immunoglobulin replacement therapy, administered intravenously or subcutaneously, along with infection prevention strategies and early intervention for bacterial infections, are the mainstays of treatment.

There is an inherent exclusionary nature to CVID. Many IEIs occur in childhood, children often contract viral illnesses that are treated as bacterial infections, and young children may not have received all childhood vaccines when they are evaluated. Therefore, ruling out other etiologies can be particularly challenging in pediatric patients. Under four-year-old children diagnosed with CVID often require periodic re-evaluation of this diagnosis [19].

CVID evaluation requires defining "poor vaccine responses" as part of its evaluation. Both T-dependent and T-independent vaccine responses are assessed by consensus diagnostic criteria. For some T-dependent vaccines, such as tetanus (0.15 IU/mL) and Haemophilus Influenzae type B (1 g/mL), there are established values at which one is considered protected or responsive. Vaccines independent of T are most commonly found in pneumococcal vaccines, such as Pneumovax, a 23-valent vaccine. It is necessary to measure titters at baseline and four to eight weeks post-vaccination in order to assess an individual's response to Pneumovax. The response to specific strains of Streptococcus pneumoniae included in the vaccine varies from population to population based on the level of 1.3 g/mL or the four-fold increase in titter. Protective responses to 70% of the S. pneumoniae. strains in those 6 years of age and older and 50% of the *S. pneumoniae*. strains in children 2 - 5 years of age, are used to define normal polysaccharide vaccine responses; however, clinicians should also consider the individual's clinical history [20].

CVID and many IEI are characterized by recurrent or severe

infection, but there is a growing body of literature elucidating non-infectious symptoms. As non-infectious complications can adversely affect quality of life as well as long-term outcomes, they are of significant consequence. From 1974 onwards did not have infectious manifestations, with 33.25 percent having autoimmune complications. A similar proportion of CVID patients on the European Society for Immunodeficiencies registry had autoimmune manifestations. As far as autoimmune manifestations go, Evan's syndrome and immune thrombocytopenic purpura (ITP) are the most common. CVID also causes arthritis, autoimmune thyroid disease, pernicious anaemia, pancreatitis, myasthenia gravis, SLE, antiphospholipid antibody syndrome, vasculitis, type 1 diabetes, and lichen planus. A thorough clinical history and relevant laboratory testing may delay the diagnosis of CVID if autoimmunity manifests before infections and predates infections. Additionally previous authorsreported that a substantial percentage of patients had other non-infectious complications, including: (1) chronic lung disease, with bronchiectasis and interstitial lung disease being the most prominent, and affecting 30.3% of patients; (2) gastrointestinal and bowel disease, characterized by villous atrophy, intraepithelial lymphocytosis, and absence of plasma cells, among other histopathologic findings, and affecting roughly 17% of patients; (3) liver disease, characterized by granulomas and/or nodular regenerative hyperplasia, affecting 12.7% of patients; (4) lymphoproliferative disease such as lymphoid hyperplasia and/or splenomegaly, affecting 20.9%; and (5) lymphoma, affecting 6.7%. Immunoglobulin replacement therapy, while providing protection from infection, is not therapeutic for these non-infectious complications, nor does it prevent development of these non-infectious complications. According to Yamashita et al. CVID patients with any non-infectious complication have an 11-fold higher risk of death than those with CVID and only infectious complications. Mortality was strongly associated with the presence of chronic lung disease, lymphoma, hepatitis, and gastrointestinal disease, but not with autoimmunity or bronchiectasis [21].

While CVID was historically thought to be a single disorder, these non-infectious complications serve to underscore that CVID presents a range of clinical symptoms that vary from individual to individual. Additionally, the application of genetic sequencing in recent decades has allowed for reclassification of a subset of patients previously diagnosed with CVID based on consensus criteria, but who were later found to have an identifiable monogenic cause of disease or variants in genes associated with poor B cell maturation and survival (e.g., Transmembrane Activator and CAML Interactor (TACI). These findings have prompted a redefining of CVID, not as a single diagnosis but rather as a phenotype that encompasses several hypogammaglobulinemia syndromes (Figure 1).

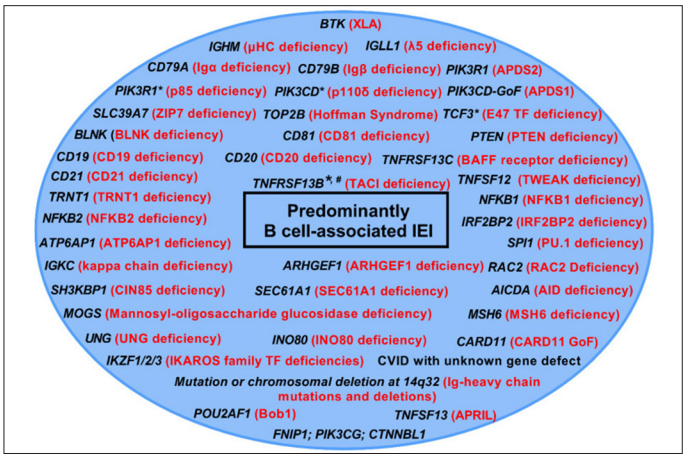

Figure 1: Listing of predominantly B cell associated IEI [2].

Future

Allogeneic hematopoietic stem cell transplantation (HSCT)

Primary B cell deficiencies can also be treated with allogenic HSCT as a curative therapy. Up to this point, immunoglobulin replacement therapy and/or antimicrobial prophylaxis have been the dominant paradigm for dealing with defects in the humoral immune compartment. Aichi virus and chronic norovirus may require more extensive treatment, such as HSCT, due to the difficulty in clearing these viruses in XLA. A high mortality rate associated with HSCT has tempered enthusiasm for this approach in patients with humoral insufficiency, despite the fact that it is currently the only useful option for patients suffering from intractable complications like refractory cytopenia despite long-term immunoglobulin replacement [22].

Therapeutic IgA

Study results showed that even with regular Ig replacement therapy, 47% of 168 XLA patients acquired chronic lung disease and bronchiectasis by age 50 despite regular Ig replacement therapy. The overall survival rates for both XLA patients with and without CLD were significantly lower in this study compared with the general population, but this reduction was more pronounced when CLD was present. Primary B cell IEI is also associated with gastrointestinal pathologies. It is not entirely surprising, since the GI tract is constantly exposed to foreign antigens, which has caused it to become the body's largest lymphoid organ. Secretory IgA (sIgA) is the predominant Ig that mediates robust protection in both respiratory and gastrointestinal tracts. It is a glycosylated tetrameric complex comprised of an IgA dimer, a J chain, and a secretory component (SC). Due to this unique structural assembly, sIgA is able to survive in a harsh mucosal environment and continually perform its immune function. As evidenced in recent years, sIgA aids in regulating microbial flora in the gut, preventing dysbiosis and maintaining gut health. Since IgA accounts for only a small fraction of FDA-approved Ig replacement products, and Ig replacement products are made from human plasma/serum, where IgA resides as a monomer instead of sIgA, it is not surprising that many B cell IEI patients develop GI pathology and develop CLD despite lifelong Ig replacement therapy [23]. Despite attempts at IgA replacement therapy in humans, this approach has been variable in effectiveness because IgA is normally transported to the mucosa from its site of local production and not through the blood stream. It is nevertheless evident that there have been incremental, albeit critical, advances in IgA biology relating to glyco-engineering and recombinant DNA expression technologies that raise the likelihood that sIgA replacement therapy will become a standard of care in the future for B cell IEI patients. Scientific bottlenecks in this regard, which are being actively addressed, include engineering the association of IgA with neonatal Fc receptors in order to extend IgA's half-life. In order to assess the feasibility of commercial scale production, sIgA will be generated in a variety of eukaryotic expression systems, such as plants, for oral consumption. We are also investigating the feasibility of coupling polymerized human plasma-derived IgA with recombinant SC to produce sIgA molecules that are both protease-resistant and fully functional *in vivo*. It will also be necessary to conduct additional research to determine the benefit of supplementing novel Ig replacement products with molecules such as recombinant hyaluronidase, which might facilitate tissue uptake, similar to what is currently available with supplemental IgG products. A therapeutic IgA approach could potentially benefit not only patients who exhibit overt and frank humoral insufficiency, but also individuals who display clinical signs of disease in the context of selective IgA deficiency if and

when it becomes part of the standard of care.

Gene therapy

A combination of immunoglobulin replacement and antimicrobial therapy may not be enough to treat hematopoietic disorders, and even though allogeneic HSCT offers a definitive cure for these conditions, almost two-thirds of transplant patients are unable to receive allogeneic HLA-matched donors. Allogeneic HSCT has a success rate almost 90% for patients who have a sibling or family member who matches their HLA. However, when the donor is unrelated or haploidentical, this statistic drops to less than 70%, and when the donor is unrelated, it plummets to less than 50%, due to complications such as graft-versus-host disease (GvHD) and immunosuppression-mediated infections [24]. This is where gene therapy can be an appropriate and potentially reasonable alternative. Adenosine deaminase deficiency and X-linked severe combined immunodeficiency are two monogenic IEIs for which gene therapy has been successfully implemented in the past two decades. By using viral vectors that carry the correct transgene of interest, autologous HSC are ex vivo transduced, followed by adoption of the transduced HSC. Over the years, clinical trials have improved viral vector design, which has reduced the risk of leukemia from insertional mutagenesis, thereby improving the safety profile of this approach. The ability to cryopreserve and transport the transduced cells has also advanced gene therapy closer to greater clinical applications, and phase I/II clinical trials have also been initiated for other IEI such as chronic granulomatous disease (CGD) and Wiskott–Aldrich Syndrome (WAS). Safety and efficacy concerns persist, however, and must be systematically addressed before this therapeutic option can be widely adopted. Aside from that, gene therapy is quite expensive at the moment. It will therefore be necessary to develop business models that address both cost-effectiveness at the production end (without compromising quality), and affordability at the patient and physician levels [25].

Gene editing

The discovery and identification of homology-directed gene editing, which offers the tantalizing possibility of repairing genetic defects *in situ*, is one of the most exciting new developments in translational genomics. The benefit of this approach is that the risk of insertional mutagenesis would be reduced, as would the physiologically appropriate regulation of gene expression. There has been a rapid advancement in gene editing in the last two years, and within the scientific paradigm of discovery, optimization, and deployment (into clinical practice), gene editing has currently landed within the arena of optimization. The clinical study phase is now underway, and several preclinical studies are being conducted that examine safety, efficacy, timing, dosage, and intracellular delivery of editing agents. de la Morena et al. [26] recently described their experience editing the BTK locus, indicating that adding the BTK terminal intron to the donor template increased BTK expression significantly. Moreover, the authors speculated that a fraction of edited hematopoietic stem cells may be able to cure the underlying immunodeficiency based on the survival advantage of BTK+ B cells. The type of cells to use (hematopoietic stem cells or induced pluripotent stem cells) for long-term self-renewal capacity of the in vitro manipulated cell population following transfer into the host is another crucial aspect of gene editing as it approaches the stage of clinical testing [26].

Current and Future Challenges

Clinical immunologists, geneticists, and laboratory immunologists must collaborate to advance clinical immunology. Increasing ease of genetic testing and the advancement of targeted therapies have ushered in an era of clinical immunology in which accurate genetic diagnosis is a greater requirement in order to improve treatments, provide counselling, and understand patients' prognoses. Additionally, new challenges have emerged in diagnostics, therapeutics, and bioethics [2]. Diagnosis is a challenge, as multigenic disorders, mosaics, somatic, and epigenetic disease-causing variants cannot be identified. Keeping genomic libraries updated, improving diagnostic accuracy, and distinguishing disease-causing variants from variants of uncertain significance require advances in bioinformatics. To define observed genetic changes as disease-causing variants, specialized in vitro testing beyond what is available commercially is also necessary but is usually only available at academic research institutions. Diagnoses and treatment of IEI require an understanding of disease pathogenesis and personalized approaches that are not supported by large studies or evidence-based medicine. Newborn screening for SCID, for example, raises ethical concerns, as it may detect other diseases without achieving any clear benefit [27].

Conclusions

Through the evaluation of patients with primary B cell IEI, the readers would gain a wealth of fundamental knowledge about the biology of the B cell. It will be most informative to combine this information with advances in genomics, systems immunology, and computational biology in the future, as we identify more patients with novel primary B cell IEI and gain a better understanding of the spectrum of clinical phenotypes that can be associated with these disorders. It might then be possible to re-purpose our understanding of B cells in order to develop new treatments and cures for diseases, just as CAR-T cell therapy has revolutionized the way certain malignancies that were once considered untreatable are now managed.

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None.

Conflict of Interest

None.

References

1. Smith T, Cunningham-Rundles C (2018) Primary B-cell immunodeficiencies. Hum Immunol 80: 351-362. https://doi.org/10.1016/j.humimm.2018.10.015
2. Ahmed A, Lippner E, Khanolkar A (2022) Clinical aspects of B cell immunodeficiencies: the past, the present and the future. Cell 11: 1-18. https://doi.org/10.3390/cells11213353
3. Bruton OC (1952) Agammaglobulinemia. Pediatrics 9: 722–728. https://doi.org/10.1542/peds.9.6.722
4. Tsukada S, Saffran DC, Rawlings DJ, Parolini O, Allen RC, et al. (1993) Deficient expression of a B cell cytoplasmic tyrosine kinase in human X-linked agammaglobulinemia. Cell 7: 279-290. https://doi.org/10.1016/0092-8674(93)90667-F
5. Vetrie D, Vořechovský I, Sideras P, Holland J, Davies A, et al. (1993) The gene involved in X-linked agammaglobulinaemia is a member of the src family of protein-tyrosine kinases. Nature 361: 226-233. https://doi.org/10.1038/361226a0
6. Smith CI, Baskin B, Humire-Greiff P, Zhou JN, Olsson PG, et al. (1994) Expression of Bruton's agammaglobulinemia tyrosine kinase gene, BTK, is selectively down-regulated in T lymphocytes and plasma cells. J Immunol 152: 557-565. https://doi.org/10.4049/jimmunol.152.2.557
7. Durandy A, Kracker S, Fischer A (2015) Chapter 25-Immune Deficiencies Caused by B Cell Defects. In Alt FW, Honjo T, Radbruch A, Reth M (eds) Molecular Biology of B Cells. Academic Press, London, UK, pp 463-479.
8. Horwood NJ, Mahon T, McDaid JP, Campbell J, Mano H, et al. (2003) Bruton's tyrosine kinase is required for lipopolysaccharide-induced tumor necrosis factor α production. J Exp Med 197: 1603-1611. https://doi.org/10.1084/jem.20021845

9. Jefferies CA, Doyle S, Brunner C, Dunne A, Brint E, et al. (2003) Bruton's tyrosine kinase is a toll/interleukin-1 receptor domain-binding protein that participates in nuclear factor κB activation by toll-like receptor 4. J Biol Chem 278: 26258-26264. https://doi.org/10.1074/jbc.M301484200

10. Bousfiha A, Jeddane L, Picard C, Al-Herz W, Ailal F, et al. (2020) Human inborn errors of immunity: 2019 update of the IUIS phenotypical classification. J Clin Immunol 40: 66-81. https://doi.org/10.1007/s10875-020-00758-x

11. Tangye SG, Al-Herz W, Bousfiha A, Chatila T, Cunningham-Rundles C, et al. (2020) Human inborn errors of immunity: 2019 update on the classification from the International union of immunological societies expert committee. J Clin Immunol 40: 24-64. https://doi.org/10.1007/s10875-019-00737-x

12. Tangye SG, Al-Herz W, Bousfiha A, Cunningham-Rundles C, Franco JL, et al. (2021) The ever-increasing array of novel inborn errors of immunity: an interim update by the IUIS committee. J Clin Immunol 41: 666-679. https://doi.org/10.1007/s10875-021-00980-1

13. Tangye SG, Al-Herz W, Bousfiha A, Cunningham-Rundles C, Franco JL, et al. (2022) Human inborn errors of immunity: 2022 update on the classification from the international union of immunological societies expert committee. J Clin Immunol 42: 1473-1507. https://doi.org/10.1007/s10875-022-01289-3

14. Le Coz C, Nguyen DN, Su C, Nolan BE, Albrecht AV, et al. (2021) Constrained chromatin accessibility in PU. 1-mutated agammaglobulinemia patients. J Exp Med 218: 1-20. https://doi.org/10.1084/jem.20201750

15. Read KA, Jones DM, Freud AG, Oestreich KJ (2021) Established and emergent roles for Ikaros transcription factors in lymphoid cell development and function. Immunol Rev 300: 82-99. https://doi.org/10.1111/imr.12936

16. Nunes-Santos CJ, Kuehn HS, Rosenzweig SD (2020) IKAROS family zinc finger 1–associated diseases in primary immunodeficiency patients. Immunol Allergy Clin 40: 461-470. https://doi.org/10.1016/j.iac.2020.04.004

17. Kuehn HS, Niemela JE, Stoddard J, Mannurita SC, Shahin T, et al. (2021) Germline IKAROS dimerization haploinsufficiency causes hematologic cytopenias and malignancies. Blood 137: 349-363. https://doi.org/10.1182/blood.2020007292

18. Hoshino A, Boutboul D, Zhang Y, Kuehn HS, Hadjadj J, et al. (2022) Gain-of-function IKZF1 variants in humans cause immune dysregulation associated with abnormal T/B cell late differentiation. Sci Immunol 7: 1-14. https://doi.org/10.1126/sciimmunol.abi7160

19. Hetemäki I, Kaustio M, Kinnunen M, Heikkilä N, Keskitalo S, et al. (2021) Loss-of-function mutation in IKZF2 leads to immunodeficiency with dysregulated germinal center reactions and reduction of MAIT cells. Sci Immunol 6: 1-17. https://doi.org/10.1126/sciimmunol.abe3454

20. Shahin T, Mayr D, Shoeb MR, Kuehn HS, Hoeger B, et al. (2022) Identification of germline monoallelic mutations in IKZF2 in patients with immune dysregulation. Blood Adv 6: 2444-2451. https://doi.org/10.1182/bloodadvances.2021006367

21. Yamashita M, Kuehn HS, Okuyama K, Okada S, Inoue Y, et al. (2021) A variant in human AIOLOS impairs adaptive immunity by interfering with IKAROS. Nat Immunol 22: 893-903. https://doi.org/10.1038/s41590-021-00951-z

22. Kuehn HS, Chang J, Yamashita M, Niemela JE, Zou C, et al. (2021) T and B cell abnormalities, pneumocystis pneumonia, and chronic lymphocytic leukemia associated with an AIOLOS defect in patients. J Exp Med 218: 1-25.

23. Yazdani R, Fekrvand S, Shahkarami S, Azizi G, Moazzami B, et al. (2019) The hyper IgM syndromes: epidemiology, pathogenesis, clinical manifestations, diagnosis and management. Clin Immunol 198: 19-30. https://doi.org/10.1016/j.clim.2018.11.007

24. Leiva LE, Junprasert J, Hollenbaugh D, Sorensen RU (1998) Central nervous system toxoplasmosis with an increased proportion of circulating γδ t cells in a patient with hyper-IgM syndrome. J Clin Immunol 18: 283-290. https://doi.org/10.1023/A:1027337923709

25. Lee MY, Chung JH, Shin JH, Hwang TJ, Kim KS, et al. (2001) Lymphonodular cryptococcosis diagnosed by fine needle aspiration cytology in hyper-IgM syndrome. a case report. Acta Cytol 45: 241-244.

26. de la Morena MT, Leonard D, Torgerson TR, Cabral-Marques O, Slatter M, et al. (2017) Long-term outcomes of 176 patients with X-linked hyper-IgM syndrome treated with or without hematopoietic cell transplantation. J Allergy Clin Immunol 139: 1282-1292. https://doi.org/10.1016/j.jaci.2016.07.039

27. Liu X, Zhou K, Yu D, Cai X, Hua Y, et al. (2017) A delayed diagnosis of X-linked hyper IgM syndrome complicated with toxoplasmic encephalitis in a child: a case report and literature review. Medicine 96: 1-7. https://doi.org/10.1097/MD.0000000000008989