

Management of Inborn Errors of Immunity in the Genomic Era

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ABSTRACT

Inborn errors of immunity are a group of rare diseases characterized by a wide variety of manifestations, including unusually severe infections, cancer susceptibility, and exaggerated inflammation that disrupts organ function. As of 2022, over 450 gene deficiencies have been classified under ten categories, where numbers are constantly increasing. The range of inborn errors of immunity varies considerably, from mild infections to serious multisystemic disease. Whereas patients with T cell defects are liable to a broad range of pathogens, selected inborn errors of immunity may predispose hosts merely to a narrow range of microorganisms. Dysregulated immune responses often cause autoimmune manifestations that may target any organ or lead to severe allergies. Therefore, presentation to any medical discipline is possible. Historically, inborn errors of immunity have been associated with short life expectancy and poor life quality, but intensive research into the field has revolutionized this assumption. Especially with the aid of translational investigations, our clinical practice has transformed from a predominantly phenotype-driven management into one that is reinforced by an etiology-driven therapy. This review summarizes the recent advances in molecularly targeted treatment approaches in various inborn errors of immunity conditions, with many success stories corroborating the power of genomic medicine. The principles of applications learned from these rare monogenic traits, in which the functional impact of the molecular pathways is clear-cut, may be instructive for developing basic concepts toward precision therapy of the common immune-mediated disorders, including autoimmunity, infectious diseases, and allergy, which affect mass populations.

Keywords: precision medicine, targeted therapy, genome, inborn errors of immunity, immune deficiency, gene therapy

INTRODUCTION

Inborn errors of immunity (IEI) are a group of diseases arising from genetic alterations that result in functional or developmental impairment of the immune system.¹ The term IEI has recently replaced the long-known and more restrictive designation, "primary immunodeficiency (PID)," to highlight better the breadth of associated manifestations, which is considerably more expansive than the initially recognized disease characteristics, namely the infection susceptibility.^{1,2} The spectrum of IEI ranges from asymptomatic IgA deficiency to severe combined immunodeficiency (SCID) that causes death in the first two years of life.

As of 2022, over 450 gene defects have been identified, with ongoing research genetically characterizing many hitherto unknown disorders each year.^{1,3} It is predicted that thousands of new gene mutations will be discovered in the subsequent decades. Per genomic medicine's promise, the improved understanding of the molecular etiologies underlying these conditions opened up the potential of reversing disease processes by targeting the key driving pathways. Concurrently, the increasing numbers of available therapeutics developed for human use have expanded the repertoire of drugs that can be readily repurposed for conditions

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Received: February 1, 2022

Accepted: February 14, 2022

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Cite this article as: Demir DD, Asnaashari K, Rezaei N, Özen A. Management of inborn errors of immunity in the genomic era. *Turk Arch Pediatri.* 2022;57(2):132-145.

other than the originally designed indications.² While pharmacologic therapies primarily function by dampening unwanted immune responses or substituting a missing element, several IEI disorders can be permanently cured by cellular therapies, such as hematopoietic stem cell transplantation (HSCT) and gene therapy. The protocols for allogeneic HSCT with less toxic conditioning regimens and the development of safer gene therapy approaches permitted the cure of many traditionally untreatable diseases. Herein, we provide a summary of foundational investigations enabling molecularly targeted treatment applications to outline the basic principles of precision medicine approaches within the context of single-gene defects. The scope of the review is to give specific examples of how etiology-driven treatment approaches can improve the treatment outcomes. Therefore, we focus on the fundamental aspects of the subject and defer factual details to more comprehensive reviews elsewhere.^{1,4}

This work used an integrative review method.⁵ We referred to updated IEI classification guidelines prepared by international expert committees, position papers, and authoritative articles when selecting the disease examples that reflect significant treatment advances in the field. References of the selected review articles of each therapy model were used to specify important milestones in the field of IEI. We performed the search strategy using a free-text search (keywords) and MeSH terms for all the selected databases by searching all articles published up to January 2022. Articles published in English were considered eligible for inclusion in the report. We cited randomized clinical trials and mentioned licensed products for specific IEI disorders whenever possible. However, we did not limit our review to formally tested studies, understanding the inherent difficulties for designing clinical phase trials with rare disorders. Many examples provided here rely on off-label therapeutic use and data produced by observational studies or small-scale case series. The readers should be aware of the limitations of such work and the scope of this article.

THE EPIDEMIOLOGY AND PUBLIC HEALTH ATTRIBUTES OF THE INBORN ERRORS OF IMMUNITY

The precise prevalence is unknown, but the estimated frequency is 1/1200; IEIs, being individually rare, altogether affect millions of children worldwide.^{6,7} Globally, the prevalence varies widely in different locales, with higher rates in the Middle East and North Africa (MENA) region than in other geographies. Also, there is a considerable variability in the distribution of different disease categories across the world. For example, the relative share of combined immunodeficiencies (CIDs) is much higher in the North African countries than elsewhere. In contrast, predominantly antibody deficiencies (PADs) comprise the majority of the disease group in the Western nations. A disparity in the IEI epidemiology links consanguineous unions with the autosomal recessive genetic disorders. A recent survey reported a parental consanguinity rate of 60.5% among the patients in the MENA region, which correlated with a preponderance of autosomal recessive gene defects (65.2%) in the area.

Inborn errors of immunity should be recognized as a major public health problem based on its burden on the patients and the healthcare system. Unfortunately, the problem is

often underestimated and has not been given enough priority in the policymaking. The majority of the subjects present during childhood and are affected by a lifelong trouble.⁸ They are at a significant risk of premature death [mortality rate: 15.8%, median age at death = 62 months, interquartile range (IQR): 12-78 months],⁹ and many of those who survive develop a prolonged suffering caused by persistent and/or recurrent infections, lymphoproliferative disease and cancers, and severe inflammatory pathologies causing target organ dysfunction.¹⁰ Nevertheless, these adverse health outcomes in the pre-genomic era have been dramatically changed by modern therapeutic approaches that enabled many patients to live normally. The key steps toward improving patient outcomes include a timely diagnosis and a tailored treatment according to the patients' needs.

FACTORS RELATED TO INBORN ERRORS OF IMMUNITY HETEROGENEITY AND CONSIDERATIONS FOR THE TREATMENT PLAN

Inborn errors of immunity are currently classified under 10 categories, with each class comprising various gene deficiencies (Table 1). The etiologic investigation starts with outlining the warning signs in the patient and noting any potential feature that may indicate a specific disorder. The first-line investigations often predict the primarily disturbed immune compartment(s) (Figure 1). Despite a significant phenotypic overlap between different IEI classes, specific presenting patterns help distinguish each subset.¹¹ Failure to thrive from early infancy coupled with diarrhea and severe eczema may indicate a CID, a group of defects caused by T cell problems. Combined immune deficiencies predispose patients to all different classes of microorganisms, including viruses, bacteria, mycobacteria, fungi, and protozoa. Patients may develop life-threatening complications following live vaccines. Therefore, a generalized susceptibility to broad pathogens in one patient should raise suspicion toward CIDs.

Predominantly antibody deficiency disorders comprise the most frequent group among all IEIs. Predominantly antibody deficiency disorders often present with recurrent otitis and sinopulmonary infections, resulting in bronchiectasis. They are frequently associated with lymphoproliferation and autoimmunity. Thus, unexplained bronchiectasis or autoimmune manifestations together with hypogammaglobulinemia often point toward humoral immune deficiencies. The timing of symptom onset is an essential consideration for differentiating various PAD disorders. Whereas agammaglobulinemias present after 6 months of life, common variable immune deficiency disorders present later in childhood or even during adulthood.

Recurrent pyogenic infections, granulomatous inflammation, and poor wound healing may indicate a defect in phagocytic cells. Due to an inherent susceptibility toward mycobacteria, chronic granulomatous disease should be considered among patients who develop complications following a BCG vaccine. Likewise, deep-seated organ abscesses may indicate phagocyte dysfunction.

Many immune dysregulation syndromes combine infection susceptibility with severe autoimmunity and lymphoproliferation. In this group, excessive inflammation may affect any

Table 1. General Treatment Measures and Targeted Therapy Approaches in IEIs				
IEI Class	IgRT	HSCT	General Treatment Principles*	Examples of Targeted Therapy**
Immunodeficiencies affecting cellular and humoral immunity	Yes	For all SCID forms and many CIDs	Avoid live vaccines, antimicrobial prophylaxis as indicated, and transfuse only irradiated and CMV-blood products if needed	-PEG-ADA enzyme therapy for ADA def. -Gene therapy for ADA def. or XL-SCID
CID with associated or syndromic features	Depending on the disease	Some forms	Avoid live vaccines (for many), immunomodulators as needed	-Gene therapy for WAS. -Thymic transplantation for DGS
Predominantly antibody deficiencies	Yes	Occasionally	Avoid live vaccines (for many), antimicrobial prophylaxis, specific vaccines (e.g., pneumococcal) for selected cases, immunomodulators as needed	APDS (PIK3CD or PIK3R1 GOF): mTOR inhibitors such as rapamycin or p110δ-specific inhibitor (leniolisib)
Diseases of immune dysregulation	Depending on the disease	Many	Antimicrobials, immunomodulators, as needed	-LRBA deficiency, DEF6 deficiency, or CTLA4 haploinsufficiency: abatacept, a CTLA4-Ig fusion protein -STAT3 GOF or JAK1 GOF: JAK inhibitors
Congenital defects of phagocyte number, function, or both	For selected diseases	Many	Avoid live bacterial vaccines, antimicrobial prophylaxis, G-CSF for neutropenias	CGD and selected cases of MSMD: IFN-γ-1b (Imukin)
Defects in intrinsic and innate immunity	For selected diseases	Some forms	Avoid live vaccines (for selected cases), antimicrobial prophylaxis per disease requirements, G-CSF for WHIM	STAT1 GOF: JAK inhibitors
Autoinflammatory disorders	No	No	Depending on the disease: cytokine inhibitors, steroids, colchicine	-AGS, CANDLE, and SAVI: JAK inhibitors -Inflammasomopathies (NLRP1, NLRP3, PSTPIP1 GOF; LPIN2, MVK, WDR1, DIRA or IL1RN def.): IL-1 antagonists
Complement deficiencies	No	No	Antibiotic prophylaxis and vaccinations (pneumococcal, meningococcal) for most, immunomodulators in selected diseases	-aHUS (Factor I, Factor H, CD46 def) or CHAPLE (CD55 def.): anti-C5 inhibitor, eculizumab; -CHAPLE: eculizumab or pozelizumab (in testing). -Hereditary angioedema: C1 esterase inhibitor Tx, ecallantide, icatibant
Bone marrow failure	Some	Yes	Antibiotic prophylaxis, immunomodulators, growth factors	
Phenocopies of IEI	Possible	No	Plasmapheresis, Rituximab, cytokine supplement	

*Each class includes numerous different gene defects and general principles may not be applicable to every disease.
**Only selected examples among many treatment approaches were provided.

AGS, Aicardi-Goutières syndrome; aHUS, atypical hemolytic uremic syndrome; APDS, activated phosphoinositide 3-kinase delta syndrome; CHAPLE, Complement hyperactivation, angiopathic thrombosis and protein-losing enteropathy; CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; CGD: chronic granulomatous disease, CID, combined immune deficiency, CMV, cytomegalovirus; CTLA4, cytotoxic T lymphocyte-associated antigen; DEF6, differentially expressed in FDCP6 homolog; DGS, DiGeorge syndrome; DIRA, deficiency of the IL-1 receptor antagonist; GOF, gain of function; HSCT, hematopoietic stem cell transplantation; IEI, inborn errors of immunity; IFN-γ-1b, interferon gamma 1b; IgRT, immunoglobulin replacement therapy; IL-1, interleukin-1; IL1RN, interleukin-1 receptor antagonist; JAK, Janus Kinase; LPIN2, Lipin2; LRBA, lipopolysaccharide-responsive beige-like anchor; MSMD, Mendelian susceptibility to mycobacterial disease; MVK, Mevalonate kinase; NLRP1, NOD-like receptor family pyrin domain containing protein 1; NLRP3, NOD-like receptor family pyrin domain containing protein 3; PEG-ADA, polyethylene glycol-modified adenosine deaminase; PIK3CD, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta; PIK3R1, phosphoinositide-3-kinase regulatory subunit 1; PSTPIP1, proline-serine-threonine phosphatase-interacting protein 1; SAVI, STING-associated vasculopathy with onset in infancy; STAT1, signal transducer and activator of transcription; STAT3, signal transducer and activator of transcription, TALEN, transcription activator-like effector nuclease; WAS, Wiskott-Aldrich Syndrome; WDR1, WD repeat domain 1; XL-SCID, X-linked severe combined immune deficiency; WHIMS, Warts, Hypogammaglobulinemia, Infections and Myelokathexis Syndrome.

organ. Autoimmune endocrine disorders such as thyroiditis and diabetes mellitus, severe enteropathy, and immune-mediated cytopenias are only a few examples among the broad range of potential autoimmune manifestations linked to this group of IELs. Uncontrolled immune activation in several gene deficiencies initiates an aggressive and life-threatening syndrome called hemophagocytic lymphohistiocytosis.

Apart from these general features linked to various immune compartments, several characteristic combinations of clinical features indicate specific gene deficiencies. Such eponymous syndromes include Wiskott-Aldrich Syndrome (WAS), Hyper-IgE syndromes caused by different gene deficiencies, ataxia telangiectasia, Nijmegen breakage syndrome, Bloom syndrome, immunodeficiency with centromeric instability and facial anomalies, DiGeorge syndrome, immuno-osseous dysplasias (cartilage hair hypoplasia, Schimke, Comel-Netherton), and X-linked (XL)-dyskeratosis congenita,¹¹ among others. Each syndrome has its characteristics, but we defer the details of each condition to relevant papers because of space considerations. It should also be noted that a significant phenotypic overlap exists between different IEL classes. Considering all these characteristic features, IEL diagnosis should account for a careful and comprehensive assessment (Figure 1).

Subsequent steps aim to characterize the patient's immunological profile and establish a molecular diagnosis. Once the specific genetic defect is known, it is crucial to sort disease-specific features in the patient and explore any target organ involvement (Figure 1). Although single-gene defects produce IELs, the severity of a particular disease often varies from one subject to another, even if they carry the same particular mutation. Also, variable clinical expressivity is not infrequent, that is, one subject with a particular gene deficiency may not present the entire spectrum of the disease features. Therefore, the patient's clinical manifestations must be fully characterized before management planning. The range of infections typically correlates with the underlying gene defect and should be considered while planning the microbiological examinations and antimicrobial therapies. An encounter with a specific pathogen or preceding immunizations may be fate-determining factors. Previous therapies and how the patient responded to them are also important considerations. Guidelines designed to help manage various IEL groups help draw the general treatment outlines (Table 1).⁴ While these principles form the treatment backbone, individualized approaches can only be made after precise diagnosis.

The treatment plans should also account for the disease stage and the patient's overall well-being. Both factors are strictly linked to the timing of diagnosis, which may be established at any age and through different routes. Presymptomatic diagnosis may be possible by screening family members of a known IEL patient for that particular disease or through bulk neonatal screening programs (Figure 2). Newborn screening (NBS) for SCID has been in operation in several countries, including New Zealand, Israel, Sweden, and Germany, and offers an opportunity to identify affected cases prior to symptom onset.¹² By whatever mechanism, early diagnosis through preemptive screening is highly advantageous to the subjects because proper management can be instituted before disease complications have appeared. Following the implementation

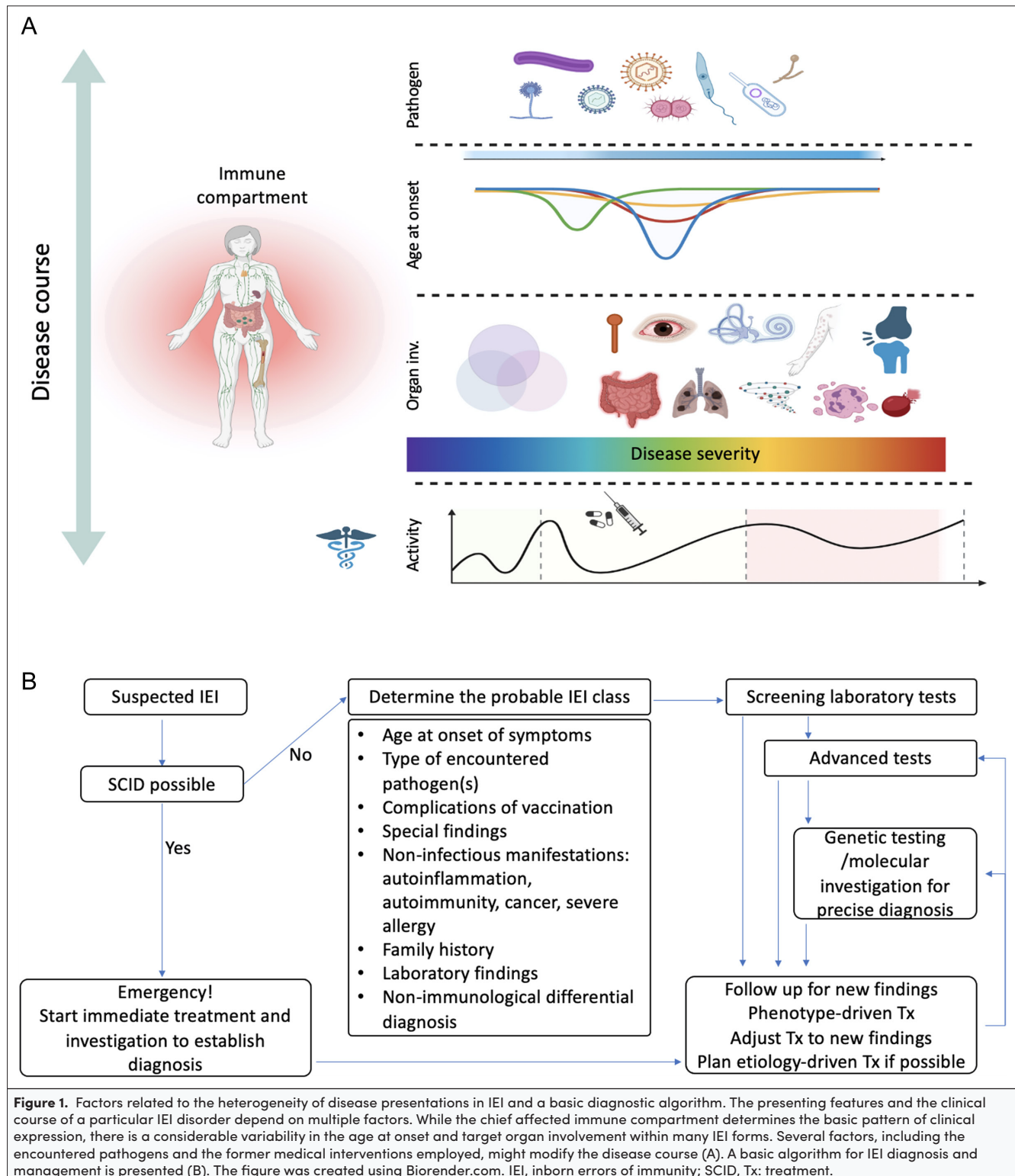
of NBS, a great majority of SCID infants have been identified at the presymptomatic phase instead of presentations by the classical infectious complications.¹² The survival rates for those infants detected by NBS and transplanted thereof were much higher than the historical controls with symptomatic diagnosis.¹² Nevertheless, most IEL patients receive the diagnosis after symptoms have developed and frequently several years later. Diagnostic delay is a considerable impediment to treatment success because permanent organ injuries may establish before diagnosis and may not be reversed despite therapy, and the treatment effect is most robust when initiated early in the disease course. Also, patients with target organ injuries may not tolerate chemotherapy regimens used for HSCT, making curative therapies inapplicable.

The recognition of the precise mechanism by which a particular gene variation produces the disease is essential for management planning. To that extent, several fundamental questions follow (Figure 3): How does the genetic variation affect the gene product, and what molecular pathway is involved? Which branch of the immune system is affected? What is the immune phenotype? How does the immunologic alteration produce tissue/organ pathology? While some gene defects affect the number of immune cells, others disrupt cellular functions (loss or gain of function) without altering cell counts. Depending on the nature of the impairment, the result may be a dampened host defense (could produce susceptibility to broad pathogens or only to a narrow range of microorganisms), excessive inflammation, or a combination of both. In other IELs, the soluble compartment of the immune system, rather than the cellular arm, is primarily disturbed, which includes cytokines, chemokines, complement products, or antibodies. These latter components play essential roles, such as biochemical signaling, immune regulation, and microbial elimination.

PRINCIPLES OF MANAGEMENT OF INBORN ERRORS OF IMMUNITY ETIOLOGY-DRIVEN VERSUS PHENOTYPE-DRIVEN THERAPIES

A multifaceted treatment plan should be made following a comprehensive evaluation that outlines the primary pathology and the associated systemic disease features. Overall, IEL management must be tailored to the patient, not to the disease. Given the breadth of modifier factors, one should balance the foreseen benefit from a particular drug or an intervention versus potential toxicity. This determination largely relies on data from previous natural history studies. The main objective of management is to target the root cause of IEL (referred to as "etiology-driven therapy" throughout the text). Besides, adjunctive therapies (referred to as "phenotype-driven therapy" throughout) aim to treat individual disease manifestations (Table 1).

Cellular therapies, including HSCT and corrective gene therapy, have been in use for several decades and possess the potential of restoring immunity in the most severe IEL diseases, with the list of indications growing. After the initial attempts to treat SCID and WAS with HSCT proved successful, this approach has been applied to many other severe IELs. Currently, HSCT is indicated in chronic granulomatous disease (CGD), major histocompatibility complex class II



deficiency, lipopolysaccharide-responsive beige-like anchor (LRBA) deficiency, activated phosphoinositide 3-kinase delta syndrome (APDS), CD40L deficiency, Purine nucleoside phosphorylase (PNP) deficiency, signal transducer and activator of transcription 1 (STAT1) gain of function (GOF), and IPEX syndrome (immune dysregulation, polyendocrinopathy,

enteropathy, X-linked), among many other gene deficiencies. Cell therapies are desirable whenever applicable because a single intervention resolves diverse systemic pathologies in the patient and permanently changes the natural disease course. While HSCT and gene therapy fields have immensely advanced since their institution several decades ago, most significant

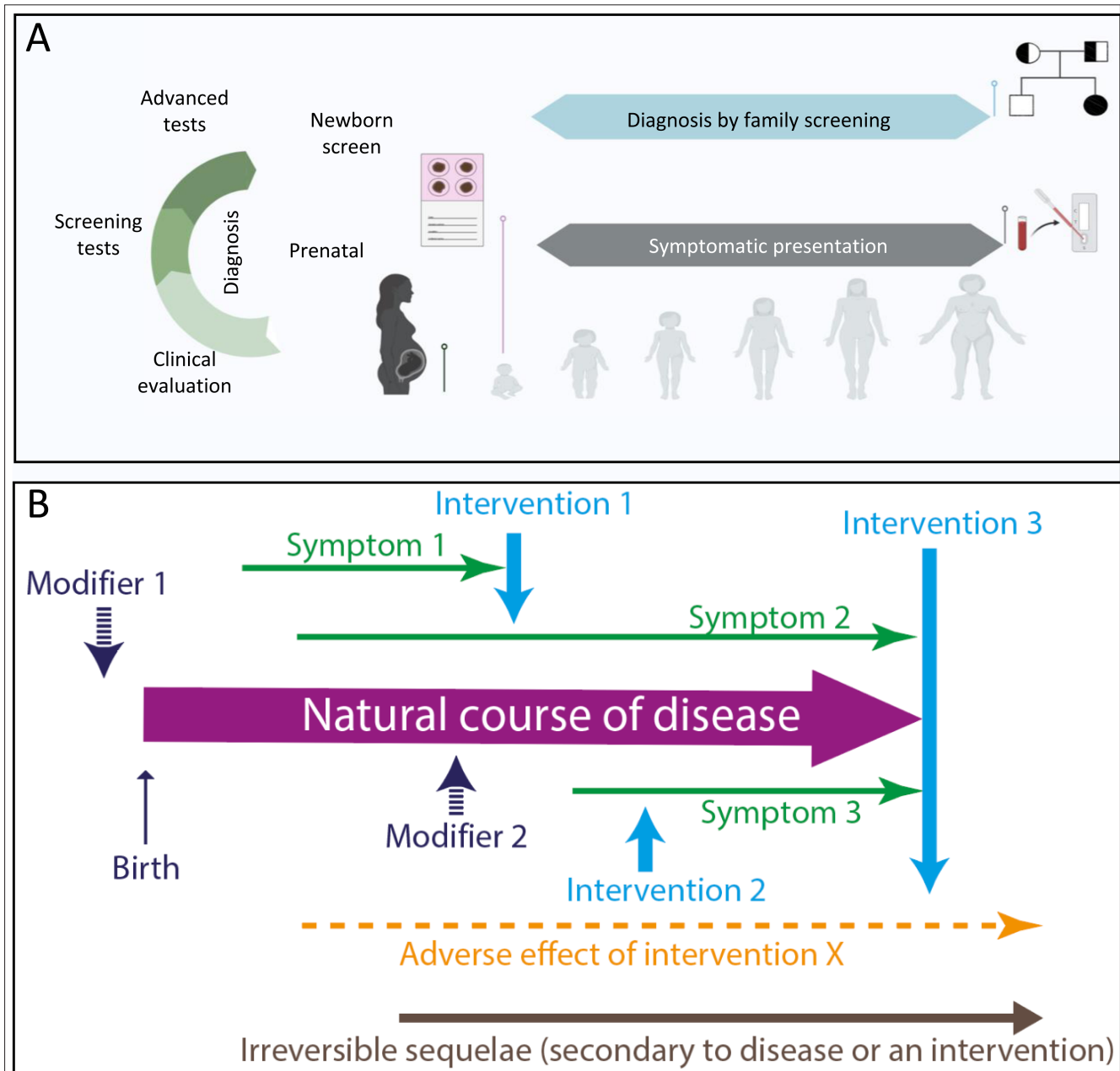


Figure 2. Possible ways of IEL diagnosis and the model of treatment effect by various interventions on the IEL course. The timing of diagnosis is a critical factor that determines disease outcome and can occur in multiple ways, as indicated (A). A schematic of potential factors that can modify the symptomatology and the natural history of an IEL disease is shown. The efficacy of different therapeutics may vary for a given disorder, with no treatment effect to partial response in certain aspects, or with the capacity to change the natural course of the disease. Intervention 3 in this example may represent an etiology-driven therapy, and intervention 1 may be a phenotype-driven therapy that relieves only a component of the disease (B). The figure was created using Biorender.com. IEL, inborn errors of immunity.

progress in pathway-specific pharmacotherapy methods has been made during the recent years. This approach relies on precise molecular diagnosis and dramatically benefits from the genome medicine and translational research. An etiology-driven pharmacotherapy could employ small-molecule inhibitors, recombinant or plasma-derived agents, and monoclonal antibodies. The antibodies can be designed to recognize specific biomolecular structures. Upon binding, they may act by neutralizing a soluble target, eliminating a cell that expresses the ligand, or blocking a biological process by inhibiting a receptor.

Unlike the corrective therapy applications in which the treatment effect is broad, phenotype-driven therapies often exhibit a narrower effect concerning the breadth of entire system manifestations and offer no/little potential to alter the natural disease history. For example, steroids or other immunosuppressive therapies carry a capacity to suppress an autoimmune manifestation in IPEX syndrome caused by the *FOXP3* gene mutations, but these agents would not treat the entire disease features. Also, the treatment effect is often temporary. Therefore, the definitive therapy in IPEX is stem cell transplantation. Many phenotype-driven therapies are used as a bridge

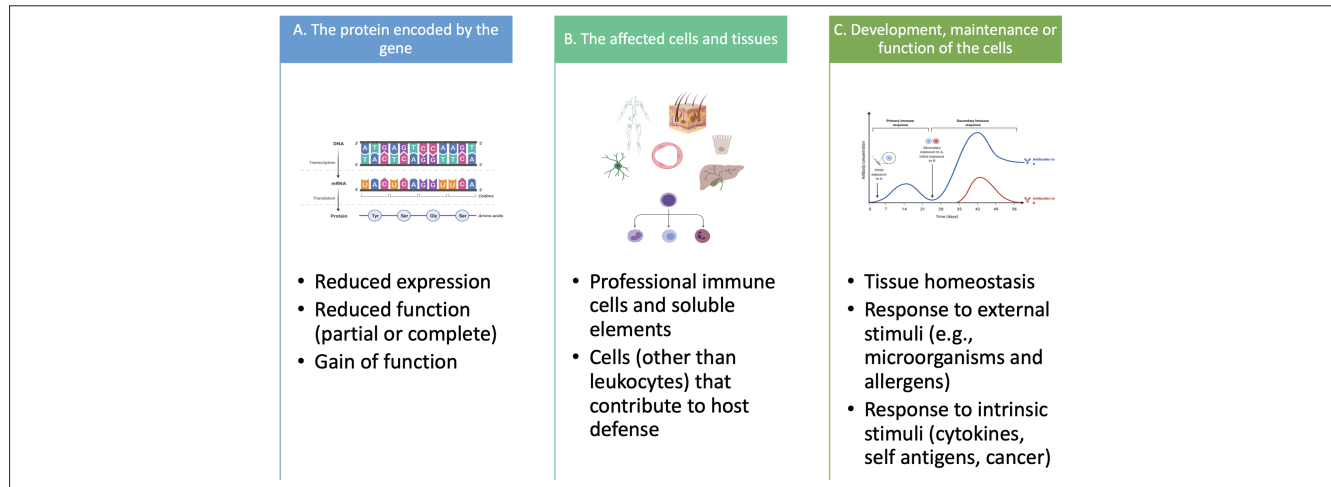


Figure 3. Depiction of the possible mechanisms by which various gene mutations cause IEI. A gene mutation underlying an IEI may alter the gene product (protein) in different ways (A). This alteration may affect professional immune cells or the soluble components of the immune system. Occasionally, impaired functions of the non-professional cells that contribute to host immunity may also cause IEI (B). The clinical manifestations of IEI are produced by abnormalities in the development, maintenance, or function of the affected compartments. While insufficient immune responses predispose the host to infections or cancer, dysregulated immune reactions produce exaggerated inflammation, resulting in autoimmunity or severe allergies (C). The figure was created using Biorender.com. IEI: Inborn errors of immunity.

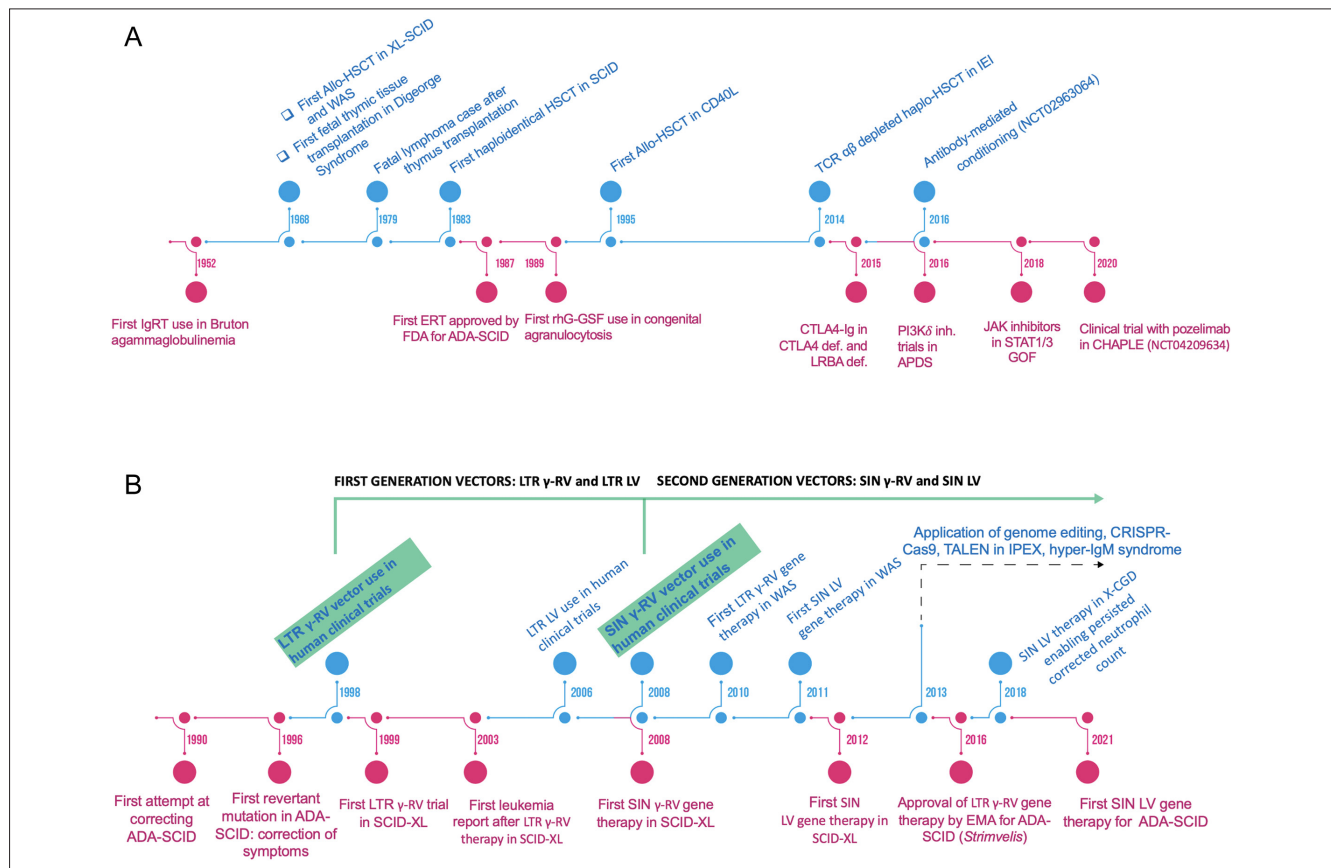


Figure 4. Timeline showing the major advances in the cellular therapies, pharmacotherapy, and the gene therapy approaches in various IEI disorders. (A) The curative treatment approaches toward IELs using cellular therapies date back to 1960s. In subsequent years, considerable advances in the field were made; for example, the successful application of haploidentical transplantation and less toxic conditioning regimens broadened the use of cellular therapies including IELs and non-IEI metabolic disorders (top panel). Selected examples of etiologically targeted pharmacologic treatment approaches in IEI are presented (bottom panel). (B) Corrective gene therapy approaches used in IEI treatment are summarized. ADA, adenosine deaminase; APDS, activated phosphoinositide 3-kinase delta syndrome; CGD, chronic granulomatous disease; GOF, gain of function; HSCT, hematopoietic stem cell transplantation; IEI, Inborn errors of immunity; IgRT, immunoglobulin replacement therapy; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked; JAK, Janus kinase; LAD, leukocyte adhesion defect; LRBA, lipopolysaccharide-responsive beige-like anchor; LTR, long terminal repeat; LV-gene therapy, lentiviral gene therapy; rhG-CSF, recombinant human granulocyte colony-stimulating factor; SCID, severe combined immune deficiency; SIN, self-inactivating; STAT, signal transducer and activator of transcription; TALEN, transcription activator-like effector nucleases; TCR, T cell receptor; γRV-gene therapy, γ retroviral gene therapy; WAS, Wiskott-Aldrich Syndrome; XL-SCID, X-linked SCID.

treatment until definitive therapies are provided; both modalities may be used adjunctly to control individual manifestations. In the subsequent section, we provide historical perspectives on how various therapeutic modalities evolved over time and specific examples showing how the precision medicine field matured our medical practice.

A HISTORIC PERSPECTIVE TO THE LANDMARKS IN MANAGEMENT OF INBORN ERRORS OF IMMUNITY

Hematopoietic Stem Cell Transplantation Still a Long-Lasting Solution to Insoluble Inborn Errors of Immunity

Allogeneic HSCT is the first of its kind for a treatment method to cure a congenital life-incompatible immune disorder. It is still considered the most potent life-saving modality among any treatment approach when considering the breadth and severity of the conditions it can cure. Today, the HSCT protocols are still evolving to best adapt to the continuously growing list of indications (Figure 4A). The first curative treatment used for IEI was allogeneic HSCT from human leukocyte antigen (HLA)-identical sibling performed on XL-SCID patients in 1968, 1 year after the initial discovery of HLA in 1967.¹³ There were also other attempts to correct various immunodeficiencies during those years. Indeed, one of the transplantation of a HLA identical marrow from a sister to a WAS patient using myeloablation has achieved success.¹⁴ During that period of the historical timeline, the lack of understanding in immunology principles and shortage of cell depletion methods from the donor have precluded HLA non-identical transplantations. With the utilization of successful techniques for T cell depletion from the donor bone marrow in animals, after that, in the early 1980s, a considerable amount of HLA-mismatch allogeneic transplantation was reported.¹⁵⁻¹⁹ In most cases, conditioning was provided by irradiation and alkylating chemotherapy. In 1986, Fischer et al²⁰ published a retrospective study to evaluate allogeneic bone marrow transplantation in immunodeficiencies performed between 1968 and 1986. Bone marrow transplantation was made for various immunodeficiency syndromes, including SCID, CID, WAS, and phagocytic cell disorders. While survival rates after HLA-matched and T cell-depleted HLA-mismatched transplants were similar in success, HLA-mismatched transplants without a T cell depletion had a poor outcome.

Although the HSCT seems like the optimal solution we have had, complications due to T cell depletion methods could sometimes outweigh the benefits. Conditioning of allogeneic stem cell sources is one of the principal methods for successful transplantation, allowing stable engraftment of donor-derived HSCs. A combination of radiotherapy and chemotherapy is classically used for most preparing regimens, but this approach potentially causes severe side effects.²¹ Acute and late toxicities include graft rejections, infections, and graft versus host disease (GVHD), negatively affecting prognosis and survival. Therefore, alternative donor and graft manipulation strategies have come into use for various IEI.²²

At first, in the 2000s, the concept of selective T cell receptor (TCR) $\alpha\beta$ -depleted haploidentical HSCs came to the fore in transplantation to prevent GVHD and increase the anti-leukemic/anti-tumor effect of the graft in case of lack of an

available HLA-matched donor.²³ This cellular modality was applied to 10 patients with SCID, IPEX, and DOCK8 mutated hyper-IgE syndrome in 2014.²⁴ Although extensive clinical data have suggested that there is no significant difference in outcomes between TCR $\alpha\beta$ -depleted haploidentical HSCT and haploidentical HSCT with immediate use of immunosuppressants,²⁵ TCR $\alpha\beta$ -depleted haplo-HSCT is still effective and can be a less toxic option for children with life-threatening immune deficiencies.

Recently, monoclonal antibody-based conditioning regimens have been developed for haploidentical transplantation with limited toxicity and provided consistent engraftment of transplanted HSC.²⁶ Several selected antibody conditioning regimens are tested in animals and include anti-CD47 to block dominant anti-phagocytic signal, anti-CD117 antibody to target HSCs, anti-CD122/IL2R β to eliminate host natural killer cells, and anti-CD40L to inhibit activated T cells; few are being tested in clinical trials for IEIs. The safety and efficacy of engraftment using a depletion with anti-CD117 are under investigation for human SCID subjects (ClinicalTrials.gov: NCT02963064).

One of the major challenging issues about bone marrow transplantation for IEIs is the determination of eligible patients and the type of regimen. Although long-term follow-up studies continue to be published from multicenter studies, the choice of the conditioning regimen for different immunodeficiencies can be highly variable and has not been optimized yet.²⁷ Optimal individualized approaches might be standardized in the future. On the other hand, with the improvement of our understanding of the thymic nature of the immune deficiency, cellular transplants other than bone marrow-derived cells have gradually evolved. In 1968, Cleveland et al²⁸ published that fetal thymic tissue transplantation could restore normal immunologic function in DiGeorge syndrome. It was followed by other fetal thymic tissue transplantations that resulted in successful immunologic reconstitution, although some of them did not fit the complete DiGeorge description by additional syndromic features.²⁹⁻³¹ In 1999, transplantation of cultured postnatal thymus tissue in 5 patients with complete DiGeorge anomaly restored normal immune function in 4 of them.³² However, after cultured thymic transplantations, abnormal B-cell proliferation and fatal lymphoma cases have also been reported.³³ Nowadays, thymic transplantation is on the agenda for curing IEI and as a possible way to induce tolerance in solid organ transplantation.³⁴

As outlined by the historical description of the evolution of cell-based therapies, the area is still evolving. Numerous case descriptions of HSCT in the literature clearly illustrate why an etiology-driven therapy is preferable to a phenotype-driven approach. Hematopoietic stem cell transplantation is not a single treatment; the protocols, type of donor, and the degree of chimerism required to cure the disease are determined for each patient. When planning for HSCT, one should also account for the diverse cofactors described in Figure 1. The assessment of the risk versus expected benefit often warrants multidisciplinary discussions.

Disease-Specific Treatments Focusing Target Molecules

From the perspective of pharmacotherapies, immunoglobulin replacement therapy can be considered the first treatment in IEIs since the first-ever patient who had PID described by Bruton³⁵ was treated using gammaglobulin injections in 1952. This empiric approach became the standard treatment modality for patients with agammaglobulinemia and many IEIs predominantly affecting antibodies after that.³⁶ Many immunoglobulin products with different concentrations and application routes provide the necessary spectrum that covers the demand from the medical and social perspectives. Especially, the self-injectable subcutaneous forms provide a significant advantage for patients who prefer home therapy.³⁷ Apart from the PAD subgroup, immunoglobulin replacement therapy is also indicated for the CIDs and many different forms of IEI that impair humoral immunity.

In parallel with the advances in HSCT described above, the emergence of enzyme replacement therapy (ERT) and its use for adenosine deaminase deficiency (ADA-SCID) has become an important milestone in IEI management (Figure 4A). In 1987, Hershfield et al³⁸ treated 2 ADA-SCID patients with polyethylene glycol-modified ADA; ERT has since proved efficacious in restoring immune function.³⁹ Polyethylene glycol-modified adenosine deaminase has a vital role as bridge therapy while preparing patients for lasting solutions, including HSCT or gene therapy. As stated above, SCID is a pediatric emergency; as soon as a SCID diagnosis is made, the general phenotype-driven therapy should be started (Table 1). Simultaneously, all efforts should be made to make a molecular diagnosis. In the case of ADA-SCID, the etiologically driven approach is invaluable because the management significantly differs from other types of SCID. First, the availability of ERT and gene therapy for this indication makes ADA-SCID different from the other SCIDs. Second, HSCT is most successful only when an HLA-matched family donor is available. Collectively, knowing the patient has ADA-SCID changes the entire process toward a curative therapy.

Another milestone in the pharmacotherapeutic field was utilizing hematopoietic growth factors as drugs, such as recombinant human granulocyte colony-stimulating factor (rhG-CSF). Severe congenital neutropenias (SCN) are characterized by persistent bacterial deep tissue infections, sepsis, and fever, accompanied by low absolute neutrophil count. Examples of gene defects causing congenital neutropenia include ELA2, HAX1, GFI1, JAGN1, G6PC3, and CSF3R.⁴⁰⁻⁴² With the development of purification methods, subsequent use of the rhG-CSF in 1989 and 1995 enabled patients with severe chronic neutropenias to acquire a healthy life. Indeed, this therapy opened up a new era for congenital or acquired phagocytic disorders.^{43,44} Yet, the etiology-driven therapy provides the best success because rhG-CSF responsiveness, cancer propensity, and comorbidities differ between the SCN types.

No doubt elucidating the molecular bases of IEI has enabled pharmacotherapies to become more targeted. One of the examples of targeted precision therapy is the application of Janus kinase (JAK) inhibitors for STAT GOF mutations, a group of IEI that leads to activation of STAT-signaling cytokines and target genes, which is mainly characterized by immune dysregulation and various autoimmune manifestations such as cytopenia, interstitial lung disease (ILD), hepatitis, and

scleroderma.⁴⁵ Both STAT1 and STAT3 GOF are associated with significant morbidity and mortality and relatively poor outcomes with HSCT.^{46,47} In a recent study, patients with STAT1 and STAT3 mutation were identified and analyzed retrospectively to determine treatment indications and outcomes. Nine out of 11 STAT1-GOF patients with various manifestations including cytopenia, enteropathy, hepatitis, failure to thrive, and ILD have had significant clinical improvement with the introduction of ruxolitinib. Similarly, 5 out of 6 patients with STAT3 GOF have responded to the treatment and exhibited improvement in multiple symptoms.⁴⁸ In the example of STAT GOFs, the JAK inhibitors reverse the driver pathway and help suppress excessive inflammation. Even if HSCT may be needed for an eventual recovery in selected cases, targeted pharmacotherapy with JAK inhibitors may be used as a bridge treatment to prepare the patient for transplantation.

In addition to STAT-GOFs, a recent study shows that JAK inhibitors can also be effective in some interferonopathies, a family of constantly growing monogenic autoinflammatory disorders characterized by disruption of the homeostatic control of interferon (IFN)-mediated immune responses. Interferons are secreted in response to various triggers such as microbes and tumors. Complex immunologic control mechanisms regulate the process of IFN production and function. Likewise, any deficiency, inadequate response, and overexpression can lead to INF pathway malfunction, hence interferonopathies.⁴⁹ STING-associated vasculopathy with onset in infancy (SAVI), Aicardi-Goutières syndrome (AGS), and PRAAS (previously referred to as CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature)) are the most well-known members of the interferonopathy family. The clinical spectrum of these diseases is similar, to a large extent, as their pathogenesis is quite close to one another. Skin lesions, developmental delay, pulmonary hypertension, neurologic manifestations, myositis, and arthritis are common presentations of these diseases.^{50,51} Since 2016, the use of JAK inhibitors as potential controllers of interferonopathies was suggested, and studies found improved symptoms in patients with AGS, CANDLE, and SAVI when treated by baricitinib (a JAK1 and JAK2 inhibitor), ruxolitinib (a JAK1 and JAK2 inhibitor), and tofacitinib (JAK3 inhibitor).^{52,53} Recent studies have backed up the effectiveness of these medications with larger cohorts,^{54,55} implying that different diseases with similar pathomechanisms can be treated with this mode of therapy in the future.

Another important achievement was the advent of anti-interleukin-1 (IL-1)-based therapies that have gained currency against inflammasomopathies, defined as dysregulation of inflammasome activation hence innate immunity.⁵⁶ Since the discovery of autoinflammatory disorders, efforts have been made to introduce proper treatments to control the flares and complications of these diseases, especially the highly morbid amyloidosis. After colchicine, Nonsteroidal anti-inflammatory drug (NSAID), and corticosteroids, the advent of IL-1 antagonists was a revolution in the world of autoinflammatory disorders. Inflammasomes are intracellular protein complexes in the form of innate immune system receptors. They can induce inflammation in response to different molecules, such as microbes.⁵⁷ The proteins constructing inflammasomes can be encoded by genes mutated in autoinflammatory disorders.⁵⁸ When inflammasomes are activated,

various cytokines can be released, including the IL-1 family, the IL-6 family, the IL-17 family, the TNF family, and type 1 IFNs, and thus the inflammation process pursues.⁶⁹ When inflammasome is activated, procaspase1 is transformed into caspase1, which changes pro-IL-1 β to its active form IL-1 β . This "alarm cytokine" then enables dimerization of the IL-1 receptor accessory protein (IL-1RAcP) with the IL-1-receptor type 1 (IL-1R1). As a result of multiple interchanges, NF κ B is activated, leading to the release of many cytokines. The IL-1 receptor antagonist (IL-1-RA) inhibits the activity of IL-1RAcP and is a potent regulator of this pathway.^{60,61}

Interleukin-1 inhibitors, by different mechanisms of inhibition, can stand in the way of inflammation caused by IL-1 and hence the catastrophic results. Anakinra, canakinumab, and rilonacept are the best-known IL-1 antagonists that have opened up a new horizon in treating autoinflammatory disorders.^{62,63} Anakinra is a recombinant IL-1-RA, canakinumab neutralizes IL-1 β activity, and rilonacept performs as a soluble decoy receptor that prevents the interaction of IL-1 β with membrane receptors.^{64,65}

Mutations in genes regulating the PI3K δ /AKT/mTOR/S6K signaling axis in immune cells have been linked to APDS.⁶⁶ Activated phosphoinositide 3-kinase delta syndrome is a group of relevant IEI that arises from hyperactivated PI3K δ /AKT/mTOR/S6K signaling pathway. Heterozygous GOF mutations in *PIK3CD* cause APDS1, and mutations in *PIK3R1* lead to APDS2. Loss-of-function (LOF) mutations in *PTEN* also cause a similar phenotype, named as APDS-like (APDS-L) disease.⁶⁷ Again, clinical cohort studies have suggested that immunodeficient and immunoregulatory involvements broadly differ among patients, ranging from asymptomatic to a severe disease-causing early death.^{66,68} The manifestations include autoimmunity, non-neoplastic lymphoproliferation, lymphomas, and neurodevelopmental delay. Therefore, the management of the disease should be tailored to the individual. Before the precise mechanism was understood for this group of disorders, conventional therapies included antimicrobial prophylaxis, immunoglobulin replacement, and the use of immunosuppressant agents depending on the predominating symptoms. Autoimmune manifestations have appeared to respond well to steroids and rituximab, with cytopenia being the most common.⁶⁹ However, significant clinical heterogeneity of symptoms necessitated a more specific target. Therefore, clinical studies with targeted therapy have been trialed with sirolimus (mTOR inhibitor) or lenilolisib, a potent, selective PI3K δ inhibitor.^{70,71} While sirolimus provided a partial response and variable evidence of benefit was shown in most patients, lenilolisib was shown to elicit an improved outcome with the relief of immunoregulatory features and an increase in overall well-being.⁶⁹ An open-label trial investigates the safety of nemiralisib, an inhaled form of PI3K δ inhibitor, in patients with PI3K δ syndrome (NCT02593539).

Another group of immune dysregulation syndromes in which targeted pharmacotherapies are employed include cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) insufficiency and LRBA deficiency.⁷² Both conditions have significant overlapping features, including susceptibility to infections, severe autoimmune manifestations, and lymphoproliferation. Lipopolysaccharide-responsive beige-like anchor plays a pivotal role in the intracellular trafficking of CTLA-4, and therefore,

LRBA deficiency renders CTLA-4 susceptible to degradation. Given the pathogenic role of CTLA-4 deficiency in the immunoregulatory manifestations in both conditions, a CTLA4-Ig fusion protein, abatacept, was trialed in controlling disease-related immune dysregulation phenotypes. Long-term abatacept therapy has proved effective in most patients with LRBA deficiency and has been established as a targeted therapy until the curative HSCT is in place.⁷² Germline and de novo heterozygous mutations in CTLA4 are variable with overlapping symptoms, and disease is subject to incomplete penetrance; hence clinical involvements have highly variable severity and phenotypes. Hundreds of distinct mutations were identified.^{73,74} Generally speaking, impaired function of CTLA-4 negative regulation on T cell via several identified mutations leads to immune dysregulation. Therefore, the replacement of CTLA-4 by CTLA-4 Fc (abatacept) is used as a potential target in patients with LRBA deficiency, an anchor protein mutation that gives rise to CTLA-4 insufficiency via impairment in its cellular trafficking.⁷⁵

Another clinical study with abatacept and mTOR inhibitors (sirolimus) was designed in 2018, after noticeable improvement with administration of abatacept in patients with CTLA-4 insufficiency. In this worldwide cohort, 8 out of 13 affected mutation carriers showed recovery with receiving mTOR inhibitor, and 14 affected mutation carriers were treated with abatacept or belatacept, with an improvement in their clinical symptoms in 11.⁷⁴ However, studies have shown that divergence of symptoms has also led to divergence in treatment response. A broad international retrospective cohort study has recently been conducted to establish a stepwise approach according to dominant specific clinical manifestations of CTLA-4 insufficiency since standardized therapy is lacking.⁷³ Seven subgroups have been defined depending on patients' major clinic involvement, including cytopenias, hypogammaglobulinemia, ILDs, neurologic involvement, abnormalities in bone marrow, and gastrointestinal and skin involvement. It has been shown that patients with gastrointestinal involvement and lymphoid infiltration in central nervous system and lung benefit from abatacept treatment. While enteropathy and cytopenia have elicited effective responses with various treatments, some situations get even worse with combining some treatment modalities.⁷³ Therefore, there are still many questions that need to be answered, including indications, dosages, and durations. An investigator-driven trial has been initiated to explore the safety of the long-term application of abatacept (ABACHAI EudraCT no. 2019-000972-40; DRKS no. DRKS00017736).

Finally, a dramatic example of success using targeted pharmacotherapy with a monoclonal antibody is illustrated by the efficacy of C5 inhibitor, eculizumab, in Complement hyperactivation, angiopathic thrombosis and protein-losing enteropathy (CHAPLE) disease, which is caused by biallelic LOF mutations in the *CD55* gene. This gene encodes a membrane regulator of the complement system; defective regulation leads to complement-mediated tissue injury and produces a lethal condition. The patients suffer from significant symptoms, such as frank edema, malnutrition, hypoalbuminemia, hypogammaglobulinemia, and occasionally, systemic thrombosis associated with high mortality.⁷⁶⁻⁷⁸ A recent study systematically investigated the role of eculizumab in CHAPLE patients among 16 subjects with various *CD55* mutations and showed an extraordinary

efficacy.⁷⁹ An open-labeled clinical study is currently exploring the efficacy and safety of pozelimab, an investigational human monoclonal antibody targeting C5, in CHAPLE disease (NCT04209634). In the example of CHAPLE disease, an etiology-driven therapy with C5-blockers changes the natural history of the disease. Before the availability of this treatment, none of the conventional approaches could reverse the disease permanently. The use of a complement inhibitory agent in CHAPLE represents a new type of therapy that could not have been predicted from clinical phenotype alone because the disease is characterized by protein-losing enteropathy (PLE) associated with intestinal lymphangiectasia and no previous data linked complement activation with PLE or intestinal lymphangiectasia.

What Did We Learn from Gene Therapy? Current Insight, Long-Term Consequences

The requirement of ongoing administration of molecular-targeted pharmacotherapies is one of the challenges for chronic disorders like IEI. On the other hand, a definitive cure is desirable for any condition if possible. Gene therapy aims to recover the consequences of the disrupted gene structure of human cells to provide functional protein for people with severe diseases. Although the idea of gene therapy emerged in 1972, it took several years to characterize and integrate retroviruses into targeted cells (Figure 4B).⁸⁰ Unsurprisingly, the first gene therapy effort has attempted to correct ADA-SCID, similar to allogeneic HSCT and ERT, for a disease considered the top priority. Retroviral-mediated transfer of ADA gene has been given into the T and CD34+ progenitor cells on the umbilical cord and bone marrow to patients with ADA deficiency in 1990, 1995, 1996, subsequently. Results were ambiguous, and long-term gene expression was not optimized despite the noticeable efficacy of gene therapy for some patients with severe immunodeficiency.⁸¹⁻⁸³ After discovering spontaneous corrections in ADA-SCID and XL-SCID by reversion of mutations, several studies indicated that a small initial population of transduced cells could give rise to a sufficient amount of diversified T cells.^{84,85} Based on those observations, clinical trials for XL-SCID have been performed in patients lacking HLA-matched donors.⁸⁶⁻⁸⁸ In those trials, the vector's viral long terminal repeat (LTR) was used to facilitate the integration of the transfer plasmid sequences into the host genome. The consequences of these studies showed noticeable, clear-cut clinical benefits for patients who showed a diversified T-cell repertoire, normal T-cell-mediated immune function, and normal growth and development.⁸⁹

However, 2 to 14 years after treatment, patients under gene therapy started to report leukemias at different time points, which led to serious concerns about this first-generation vector. Analysis revealed that vector had been inserted into oncogenic loci resulting in the oncogenetic process by transactivation.⁹⁰ Removing of LTR resulted in self-inactivating (SIN) second-generation vectors either in lentivirus (LV) or γ retrovirus (γ RV)⁹¹ with a greater level of safety, and clinical trials were again initiated in Paris, London, and Boston.^{92,93} T cell reconstruction was achieved in almost all patients, and no cases of leukemia have been reported in long-term follow-up of patients treated with SIN γ RV-IL2RG vector. Today, the LTR component of lentiviruses is split together with some other

components of LVs to increase its safety during genome editing (<https://www.addgene.org/guides/lentivirus/>). One of the problems in all kinds of vector-based gene therapy was the failure to differentiate B- and NK-cells. This is thought to be caused by the absence of myeloablation and insufficient engraftment of vector-transduced cells.⁹⁴ Now, a recent multicenter study in 2019 has suggested that mild myeloablation with the use of SIN IL2RG LV vector resulted in the reconstitution of T-cell, NK-cell, and B-cell function in a patient with XL-SCID.⁹⁵ On the other hand, with the improvements in XL-SCID trials, several other IEI gene therapies are being developed simultaneously, including WAS, ADA-SCID, CGD, and leukocyte adhesion deficiency. Similar to SCID-XL, in WAS gene therapy trials, patients treated with γ RV developed myelodysplastic syndrome and leukemia at different time points.^{96,97} A subsequent clinical trial application using SIN lentiviral vector containing WASP cDNA concluded with the effective reconstruction of leukocytes including T and B cells despite the failure to correct thrombocytopenia.⁹⁸

As discussed above, the treatment outcomes of ADA-SCID have always been somewhat different from the other type of IEIs. The gene therapy journey for ADA deficiency has been around since the 1990s; however, it failed.⁹⁹ Later on, along with other SCID trials, a combination of γ RV-mediated transduction of hematopoietic progenitor cells with mild chemotherapy has succeeded and provides sufficient immune function with persistent expression of transduced B- and NK-cells, and T cell reconstruction was less effective as compared with XL-SCID.^{100,101} Importantly, unlike γ RV vector-based gene therapy for XL-SCID, there was no malignancy, although the same insertion patterns of vectors to oncogenes have been detected (NCT00794508, NCT00599781, NCT03478670, and NCT00018018). After the approval of safety and efficacy in the clinical trials, strimvelis, the first gene therapy drug product, entered the market in 2016.¹⁰² A recent investigational gene therapy composed of autologous CD34+ hematopoietic stem and progenitor cells transduced ex vivo with a SIN-LV vector encoding human ADA has been used for 50 patients with ADA-SCID. The study resulted in high overall and event-free survival with sustained ADA expression, metabolic correction, and functional immune reconstitution.¹⁰³

On the other hand, correction of CGD is more challenging since the expression of the gene does not provide a selective advantage to transduced cells.¹⁰⁴ Besides, selective myeloid expression is required in order to prevent toxicity because of the restricted gene expression of CGD.¹⁰⁴ At first, several attempts to correct XL-CGD have resulted in only transient clinical benefit.¹⁰⁵ After that, new clinical trials using chimeric myeloid promoter lentiviral vector to express specifically targeted genes to treat XL-CGD have been initiated in 2013 and 2014 (NCT01855685 and NCT02234934). Recently, Kohn et al¹⁰⁶ reported initial efficacy and safety results in 2020. Two of the IEIs in which gene therapies are still under investigation are CD40L deficiency and IPEX. For IPEX, new genetically reprogrammed techniques are on the agenda. Genome editing using site-specific endonuclease and CRISPR-Cas9 system might be a promising method for the future.¹⁰⁷ Similarly, site-specific gene editing of stem cells from CD40L deficiency using transcription activator-like effector nuclease and CRISPR-CAS9 also represent alternative treatment models.¹⁰⁸

CONCLUSION

Every day, more and more patients suffering from various IEI disorders are enjoying the successful clinical applications of precision therapy. Numerous examples of success stories unequivocally establish the power of genomic science. Meanwhile, the challenge continues with optimizing therapy outcomes for individual IEIs. We hope the concepts drawn here in the light of different examples will shed light on the complexity inherent to the subject and how Herculean efforts to overcome such hassles can conquer traditionally untreatable conditions.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – D.D.D., K.A., A.Ö.; Design – D.D.D., K.A., A.Ö.; Supervision – A.Ö., N.R.; Materials – D.D.D., K.A., A.Ö.; Data Collection and/or Processing – D.D.D., K.A., A.Ö.; Analysis and/or Interpretation – D.D.D., K.A., A.Ö.; Literature Search – D.D.D., K.A., N.R., A.Ö.; Writing Manuscript – D.D.D., K.A., A.Ö.; Critical Review – N.R., A.Ö.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

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