

Precision Medicine as Treatment for Primary Immunodeficiency and Immune Dysregulation

Rodrigo Hoyos-Bachiloglú¹, Craig D. Platt^{2*}

¹ Department of Pediatric Infectious Diseases and Immunology, Pontificia Universidad Católica de Chile, Santiago, Chile

² Division of Immunology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

Abstract

“Precision medicine” is the use of therapy that targets the molecular basis of a patient's disease process. This approach is increasingly well-established in treatment of monogenic disorders of immunity, including primary immunodeficiencies and primary immune regulatory disorders.

This is due to the exquisite detail with which many immune pathways have been defined, and the wide variety of immune modulatory medications that target these pathways. Here we review many of the most effective uses of this approach and suggest a framework for classifying these strategies.

Keywords Precision medicine, Targeted therapy, Primary immunodeficiency disease, immune dysregulation.

* Corresponding author: Craig D. Platt

E-mail: craig.platt@childrens.harvard.edu

1. Department of Pediatric Infectious Diseases and Immunology, Pontificia Universidad Católica de Chile, Santiago, Chile. 2. Division of Immunology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

Introduction

Widespread availability of “next generation” sequencing techniques, including targeted sequencing panels and whole exome sequencing has ushered in an era where monogenic causes of immunodeficiency and immune dysregulation can be determined with speed and precision. When the mechanistic basis of the disease is known, a

large and increasing repertoire of immune modulatory medications, many designed for treating common autoimmune diseases, are available for use as targeted therapies. In this review, we present a framework for classifying “precision medicine” strategies in hopes that this will aid in understanding the use of these therapies and will assist the rational design of novel targeted therapies. The precision medicine strategies dis-

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discussed below fall into one of three categories: 1) replacement of “missing molecules,” 2) inhibition of overactive intracellular signaling pathways, and 3) cytokine blockade.

Replacement of “missing molecules”

Monogenic defects frequently cause disease through disruption of the expression or function of a protein gene product. The simplest form of precision medicine, infusion of the “missing molecule” is not possible for the vast majority of disorders, considering that the precise localization of receptors, signaling molecules and other cellular components is typically necessary for their effective function. We discuss several notable exceptions below, where treatment involves supplementation of defective pathways through infusion of WT proteins. (Note that gene therapy and gene editing approaches are outside of the scope of this review, though in principle, these are the ultimate realization of this strategy).

Use of IVIG for antibody deficiency

Precision medicine was arguably part of the practice of clinical immunology since the earliest days of the field. In the same report that Ogden Bruton described agammaglobulinemia in an 8 year-old boy with recurrent pneumococcal sepsis, otitis media, and pneumonia, he described effective treatment by replacing the patient’s missing IgG with subcutaneous immunoglobulin replacement (1). Modern immunoglobulin preparations, purified and pooled from thousands of donors, are routinely used for patients with antibody deficiency. Administered via intravenous or subcutaneous infusion, immunoglobulin replacement provides levels of serum IgG comparable to those from healthy subjects (2). This is remarkably effective at reducing rate of sinopulmonary infections and preventing long-term complications such as bronchiectasis (2). While not a form of precision medicine, it should be noted that IVIG is also widely used for its immune modulatory properties. It is FDA-approved for use in im-

mune thrombocytopenic purpura and chronic inflammatory demyelinating polyneuropathy, but is used off-label for many more autoimmune and inflammatory conditions (3). IVIG does not modulate immune function through a single defined mechanism. Just a few of the proposed mechanisms include 1) blockade of Fc receptors on macrophages of the reticuloendothelial system, 2) blockade of adhesion molecules on leukocytes, 3) saturation of FcRn receptors to enhance clearance of autoantibodies and 4) induction of signaling through inhibitory FcγRIIB receptors on effector macrophages (4).

Use of PEG-ADA in adenosine deaminase deficiency SCID

In 1972, Dr. Eloise Giblett and colleagues reported two unrelated females with SCID who had no detectable adenosine-deaminase enzyme activity in their red blood-cells (5). A causal mechanism between ADA deficiency and defective lymphocyte function was defined, the first time that the molecular basis for immunodeficiency had been described. Later work elucidated that ADA deficiency is a disorder of purine metabolism that leads to accumulation of toxic metabolites that induces lymphocyte death and thymic dysfunction (6).

In 1987, Hershfield et al. described intramuscular infusion of bovine-derived ADA derived conjugated to polyethylene glycol (PEG-ADA) to treat a patient with ADA deficiency (7). This was the basis for an FDA-approved treatment for ADA-SCID through enzyme replacement. Weekly or twice-weekly intramuscular injection of PEG-ADA leads to sufficient plasma ADA levels to allow survival of lymphocyte progenitors and may also protect some ADA-deficient patients from hepatic and neurologic dysfunction (8, 9).

Approximately 80% of patients have a significant response to enzyme replacement within 2-4 months, including protection against opportunistic and life-threatening infections (9). Lymphocyte

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number and function, however, rarely return to normal levels. Even among patients with an initially robust response, a gradual decline in lymphocyte counts and function can be seen over time (9). This is in contrast to data from patients who have received HSCT or gene therapy where available data describes long-term stability of lymphocyte function.¹⁰ While not a definitive treatment strategy, for patients without immediate access to such treatments, PEG-ADA enzyme replacement remains a potentially life-saving tool.

PEG-ADA enzyme replacement therapy is unique among the precision therapies described in this review as it is a true “orphan drug,” developed to treat the small population of patients with ADA deficiency and of no utility to patients with other forms of SCID or immune dysregulation (8). Like other orphan drugs, the cost is quite high, which limits availability in resource-poor countries or in patients without access to high quality health insurance. With such medications, there is little likelihood of decreasing costs over time as there is no possibility of scaling up production or competition from generic or biosimilar products (11).

Abatacept to treat CTLA-4 Haploinsufficiency and LRBA deficiency

Cytotoxic T lymphocyte antigen 4 (CTLA-4) is a critical T cell inhibitory molecule present on activated T cells and regulatory T cells (Tregs) that restrains immune responses by interfering with T cell costimulation by antigen presenting cells. The inhibitory properties of this molecule are due to its ability to block interaction of CD28 on T cells with CD80 and CD86, essential costimulatory molecules expressed on antigen presenting cells (12).

Reduced surface expression of CTLA-4 is caused by monoallelic mutations in CTLA-4 and biallelic mutations in lipopolysaccharide-responsive beige-like anchor (LRBA), a CTLA-4 chaperone (13-16). Patients with both disorders present with humoral immunodeficiency and severe autoimmunity/im-

mune dysregulation including lymphoproliferation, immune-mediated cytopenias, enteropathy, and endocrinopathies (16). As reduced CTLA-4 surface expression on T cells underlies the pathology in these disorders, infusion of CTLA-4 Ig (abatacept), a medication FDA approved for rheumatoid arthritis, has proven an incredibly powerful approach, as discussed further below.

When LRBA deficiency was discovered in 2012 through whole exome sequencing, the molecular mechanism of the disorder was not immediately clear (17, 18). However, in a seminal 2015 paper, Lo et al. described dramatic clinical improvement in three LRBA-deficient patients treated with abatacept (13). Patients demonstrated rapid improvement in lung pathology as revealed by computed CT scan and pulmonary function testing, improvement or resolution of inflammatory and/or autoimmune conditions, and normalization of biomarkers of T cell dysregulation including soluble CD25 and percentage of peripheral naïve T cells. This initially unexpected response to abatacept led to the finding that LRBA acts as a chaperone that directs intracellular trafficking of CTLA-4 to the cell surface, preventing lysosomal degradation (13).

A recent report has examined the long-term efficacy of abatacept in 18 patients with LRBA deficiency (19). In 16 of these patients there was substantial long-term improvement. There was near complete control of lymphoproliferation and chronic diarrhea, as well as significant improvement in autoimmune cytopenias. Two biomarkers of disease activity, soluble CD25 and percentage of peripheral regulatory T cells, correlated well with response to abatacept in these patients.

As noted above, patients with CTLA-4 haploinsufficiency due to heterozygous mutations in CTLA4 can present with an autosomal dominant immune dysregulation syndrome and immunodeficiency that is strikingly similar to LRBA deficiency. A report on penetrance, clinical features, treatment strategies in 133 CTLA-4 mutation carriers documented the response 14 of these patient who received the

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CTLA-4 fusion protein abatacept or the closely related drug belatacept (20). 11 of the 14 demonstrated a strong clinical response including resolution of enteropathy, resolution of lymphoproliferation, reduced lymphadenopathy, stabilization of platelet counts, and improvement of optic neuritis (20).

Chronic granulomatous disease and IFN- γ

Initially described as “fatal granulomatous disease of childhood” the molecular basis of chronic granulomatous disease (CGD) was discovered in 1967 (21, 22). This disorder is caused by defects in the phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Pathogenic mutations in genes coding the NADPH oxidase subunits gp91phox, p22phox, p67phox or p47phox abrogate oxidase activity and compromise the immune response against specific bacteria and fungi (23). Affected patients typically present during childhood with bacterial infections such as suppurative lymphadenitis, recurrent staphylococcal infections and failure to thrive, while a small group of patients initially present with noninfectious complications like very early onset inflammatory bowel disease (24).

Survival in CGD patients has improved significantly since the 1990s and it is currently ~90% at 10 years of age (25). However, the probability of experiencing severe invasive infections remains high despite antimicrobial prophylaxis (26). A standard prophylactic regimen for patients with CGD includes the use of trimethoprim-sulfamethoxazole, itraconazole and interferon-gamma (IFN- γ) (27). Initial studies suggested that *in vitro* treatment with exogenous IFN- γ could increase superoxide production in monocytes derived from patients with CGD (28) and led to the first trials in humans subjects as a potential targeted therapy for the disease. The first human study to report the use of IFN- γ for prophylaxis in CGD patients was a randomized double-blind placebo-controlled trial conducted in the 1990s. This study of 128 patients randomly

assigned to receive IFN- γ or placebo three times a week, showed a 67% reduction in risk of developing a serious infection and a significantly shorter length of admission in patients receiving IFN- γ (29). Subgroup analyses revealed that the use of IFN- γ prophylaxis was most effective in patients younger than 10 years old and no significant difference was noted between patients with X-linked and autosomal recessive CGD (29). A subsequent long-term efficacy and toxicity study on patients receiving IFN- γ prophylaxis for up to 9 years showed that patients receiving interferon therapy do not experience life-threatening medication related adverse events. This same study reported that IFN- γ therapy reduced the rate of serious infections from a baseline of 1.1 to 0.3 per patient-year and reduced mortality to 1.5% per patient year (30). Although these data support the use of IFN- γ to prevent severe infections in CGD, it must be noted that both trials were conducted before the use of antifungals as part of routine care for CGD patients. Newer studies are needed in order to establish the role of IFN- γ therapy in CGD patients receiving optimal anti-microbial prophylaxis.

While IFN- γ has a well-established role in the activation of macrophages, the molecular basis for IFN- γ therapy in the CGD population are unclear. Data from both murine and human studies have shown that the mechanism of action does not involve an increase in the neutrophil respiratory burst (29-31). A potential mechanism is an IFN- γ -mediated increase in nitric oxide (NO) production by phagocytes in CGD patients, which may contribute to phagocyte-mediated immunity against bacterial and fungal infections (32). However, because of the numerous downstream effects of IFN- γ , its mechanism of action is likely to be multifactorial.

Mendelian susceptibility to mycobacterial diseases, IFN- α and IFN- γ

Mendelian susceptibility to mycobacterial diseases (MSMD) is a collection of monogenic disorders that predisposes affected individuals to infections

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by nontuberculous environmental mycobacteria, the Bacillus Calmette-Guérin (BCG) vaccine, Mycobacterium tuberculosis and Salmonella, while being otherwise immunocompetent (33). To date, 11 different genes have been shown to cause MSMD (IL12B, IL12RB1, ISG15, TYK2, IRF8, SPPL2A, CYBB, IFNGR1, IFNGR2, STAT1, NEMO) (34), all of which code for proteins involved in IFN- γ dependent immunity. MSMD is most frequently caused by mutations affecting IL12RB1 (44%), followed by defects in IFNGR1 (29%), IL12B (12%) and IFNGR2 (5%) (33). The high allelic heterogeneity at the 11 loci involved in MSMD causes 21 different genetic forms of the condition based on the functional defect being partial or complete, the protein being expressed or not and the mechanism causing protein dysfunction. Understanding the molecular mechanisms underlying MSMD has led to the use of recombinant IFN- γ and in some cases IFN- α , as therapeutic agents.

The IFN- γ receptor is a multimeric receptor complex consisting of two different chains: IFN γ R1 and IFN γ R2 (35). Mutations in both chains of the IFN- γ receptor can cause MSMD. Mutations affecting the IFNGR1 or IFNGR2 genes can present as complete or partial forms of IFN γ R1 and IFN γ R2 deficiency, respectively. Patients with partial forms of IFN γ R1 and IFN γ R2 deficiency express significantly reduced, but not absent, levels of protein at the cell surface that allow the cellular response to pharmacological doses of IFN- γ (36). Unlike cases of partial deficiency, patients with complete forms of IFN γ R1 and IFN γ R2 deficiency do not express residual protein and are unable to respond to either physiological or pharmacological doses of IFN- γ . IFN- γ has been used in this subset of patients, in addition to antibiotics, to control mycobacterial infections (38). Although the use of IFN- γ is based on the overlap in gene expression profiles after stimulation with IFN- γ and IFN- α (39). Its use has been associated with variable clinical responses (38-40), and it has been suggested to aggravate mycobacterial disease (41-43).

During the physiological immune response to mycobacteria, dendritic cells and phagocytes produce high amounts of IL-12, a dimer consisting of two subunits: p35 and p40. IL-12 binds to its receptor, a dimer of IL-12R γ 1 and IL-12R γ 2, on the surface of T cells and NK cells and stimulates the production of IFN- γ (33). Defects that disrupt the cross talk between phagocytes/dendritic cells and T/NK cells present as MSMD. Mutations affecting IL12RB1 are the most frequent genetic diagnosis in patients with susceptibility to mycobacterial infections, while mutations in IL12B, the gene coding for the p40 subunit of IL-12 are also common (33). These defects disrupt the cross-talk between macrophages and lymphocytes, decreasing IL-12 stimulated IFN- γ production by T and NK cells during the normal immune response to mycobacteria. Recognition of the crucial role of IL-12 in the immune response to mycobacteria and its physiological role in stimulating IFN- γ production lead to the successful use of exogenous IFN- γ to by-pass the underlying molecular defect in patients with mutations in IL12RB1 (44) and IL12B (45).

Inhibition of overactive signaling pathways

While most monogenic causes of immune deficiency and immune dysregulation are due to loss of function, an increasing number of disorders have been defined as being secondary to activating mutations, also known as “gain of function” (GOF) mutations. In such disorders, increased protein activity, or resistance to inhibitory signaling leads to elevated levels of signaling. Many of these disorders are amenable to use of small molecule therapies, originally developed as immunosuppression for more common autoimmune disorders to target the overactive signaling pathways.

STAT1 gain of function and JAK inhibitors

Signal transducer and activator of transcription (STAT) proteins are a family of intracellular transcription factors that regulate cell growth and

Archive of SID

differentiation in a wide variety of tissues and systems, including the immune system.46exemplified by the bench-to-bedside success of Jak inhibitors ('jakinibs' Under steady state conditions, STATs are found in the cytoplasm and can translocate to the nucleus after being activated. When a cell surface receptor binds its ligand, receptor associated Janus kinases (JAKs) are activated and phosphorylate the intracellular domains of the receptor, creating docking sites for STAT proteins. After binding to these docking sites, STATs are phosphorylated by JAKs, dimerize and translocate to the nucleus where they modulate the transcription of specific target genes (47). STAT1 was the first member of this family to be identified as part of type I IFN signaling and is now known to participate in several other pathways including IFN- γ , IFN- λ , IL-2, IL-3, IL-6, IL-9, IL-10, IL-11, IL-12, IL-15, IL-21, IL-22, IL-26, IL-27, EGF, VEGF, FGF, HGF, GH, angiotensin and OSM pathways (48).

Pathogenic mutations causing STAT1 deficiency were first recognized in patients with MSMD though more recently, the use of next generation sequencing technologies allowed researchers to identify heterozygous GOF mutations in STAT1 as the most frequent genetic defect causing autosomal dominant chronic mucocutaneous candidiasis (AD-CMC) (49, 50). STAT1 GOF mutations lead to increased STAT1 activation after stimulation with IFN- α , IFN- β , IFN- γ or IL-27 as a result of decreased STAT1 dephosphorylation in the nucleus (51). The enhanced cellular response to these cytokines results in increased transcription of interferon stimulated genes and impaired development of Th17 cells (49).

Recurrent infections by *Candida albicans* affecting the skin, nails or mucosae are the defining feature in patients with AD-CMC; however, bacterial infections affecting the respiratory tract and the skin are common and many patients are susceptible to EBV, HSV and mycobacterial infections. STAT1 GOF mutations are frequently associated

with autoimmune diseases including type I diabetes, autoimmune enteropathy and thyroid disease (51). Additionally, an early onset immunodeficiency polyendocrinopathy enteropathy X-linked (IPEX)-like phenotype (52) and a combined immunodeficiency phenotype have been reported (53). The immune phenotype of STAT1 GOF patients are highly variable and can include T, B and NK lymphopenia, decreased T cell function, decreased NK cell function (54) and hypogammaglobulinemia. Low memory B cells are found in 49% of patients, while 82% of patients have low in vitro production of IL-17A after PMA-ionomycin stimulation (50).

Three small molecule JAK inhibitors are currently available and FDA-approved for the treatment of rheumatoid arthritis (tofacitinib and baricitinib), as well as myelofibrosis and polycythemia vera, (ruxolitinib). An extensive understanding of JAK-STAT pathways has been fundamental for treatment of patients with autoimmune and autoinflammatory manifestations of STAT1 GOF mutations using these JAK inhibitors. The biggest series to date reports the use of ruxolitinib or tofacitinib in 11 patients, 5 of them had CMC, 6 had autoimmune cytopenias or hepatitis and 5 had autoimmune enteritis. Treatment with JAK inhibitors led to substantial improvement of autoimmune manifestations in 10 patients and resolution of CMC in all of them (55). Baricitinib has been successfully used to treat CMC and recurrent oral and vaginal ulcers in one patient (56). Additionally, in vitro treatment with JAK inhibitors has been shown to correct NK (57) and T (58) cell dysfunction in patients with STAT1 GOF mutations.

STAT3 gain of function and JAK inhibitors

STAT3 is a transcription factor that regulates genes involved in proliferation, apoptosis and differentiation and modulates cellular responses to cytokines including type I, type II and type III interferons, IL-2, IL-6, IL-7, IL-10, IL-12, IL-15, IL-21, IL-23

Archive of SID

and IL-27 (59). Mutations in STAT3 can cause loss or gain-of-function depending on the amino acid change rather than its location within the amino acid sequence (60). GOF mutations lead increased transcriptional activity due to delayed STAT3 dephosphorylation and impaired phosphorylation of STAT1 and STAT5b (61) as a consequence of negative regulation by suppressor of cytokine signaling 3 (SOCS3), a STAT3 target (62).

Germline heterozygous STAT3 GOF mutations were first identified in patients with autoimmune diseases presenting at <5 years of age or isolated type I diabetes diagnosed within the first 6 months of life (62). Since the initial description of the disease, the clinical presentation of STAT3 GOF mutations has expanded, and should now be considered in patients presenting with immune dysregulation features of other monogenic diseases including autoimmune lymphoproliferative syndrome (ALPS), IPEX-like syndromes, and STAT5b deficiency (61, 64, 65). Autoimmune cytopenias and lymphoproliferation are the most common manifestations of immune dysregulation in patients with STAT3 GOF mutations, while immunodeficiency manifests predominantly as recurrent respiratory infections (66). Immunological findings in these patients include T cell lymphopenia, hypogammaglobulinemia, increased numbers of circulating double negative T cells and decreased numbers of TH17 cells, class-switched memory B cells, NK cells and eosinophils (61, 65).

While the concept of cytokine blockade is addressed more thoroughly later in this review, use of anti-IL6 in treatment of STAT3 GOF mutation is addressed here, as the goal of treatment in this case is disruption of signaling upstream of the STAT3. In 2015, Milner et al, described this approach in a single patient using the rationale that IL-6 is one of the primary cytokines that induces signaling via STAT3 (61). Indeed, within months of starting tocilizumab, the patient demonstrated improvement of flexion contractures. Immune phenotyping also demonstrated normalization of previously elevated TH17 cell frequency. Subsequent reports described im-

provement in interstitial lung disease, arthritis, autoimmune hepatitis (55). However, control of this dysregulation is generally incomplete on tocilizumab monotherapy, and addition of JAK inhibitors, as described above, leads to better disease control (55). Particularly in difficult to treat disorders such as STAT3 GOF, approaching control from two independent mechanisms has been shown to be an effective approach.

APDS1, APDS2 and sirolimus/PI3Kγ inhibitors

Phosphatidylinositol 3-kinases (PI3Ks) are a group of signal transducer enzymes that influence multiple processes like cell cycle progression, cell growth and survival. Class IA PI3Ks are heterodimeric enzymes, composed of a regulatory (p85α) and a catalytic subunit (p110α, p110β or p110δ), that phosphorylates phosphatidylinositol (4,5)-biphosphate into phosphatidylinositol (3,4,5)-triphosphate (67). Activating mutations in for p110δ (PIK3CD) or loss of function mutations in p85α (PIK3R1) leads to increased p110δ signaling and is responsible for activated phosphoinositide 3-kinase-δ syndrome (APDS) type I (68) and II, (69) respectively.

Regardless of the mutated gene, APDS type I and II share a common pathophysiology characterized by increased levels of phosphatidylinositol (3,4,5)-triphosphate and hyperstimulation of Akt/mTOR signaling while inhibiting the FOXO family of transcription factors (67). This leads to immune dysregulation and immunodeficiency manifest by recurrent respiratory infections, bronchiectasis, predisposition to infections by herpes family viruses, lymphadenopathy, splenomegaly, increased risk of lymphoma and antibody deficiency ranging from agammaglobulinemia to hyper IgM syndrome. Immunological findings in these patients include progressive B cell lymphopenia, increased circulating transitional B cells, decreased class switched memory B cells, reduced naïve T cells and expansion of terminally differentiated effector T cells (70).

Archive of SID

Understanding the role of mTOR activation in the pathophysiology of APDS led to the use of rapamycin as the first targeted therapy for this primary immunodeficiency (71). Rapamycin, an mTOR inhibitor, targets many of the signaling pathways up-regulated by PI3K activation. Patients treated with rapamycin show reduced lymphoproliferation (72), recovery of naïve T cell counts and a decrease in number of terminally differentiated T cells (71).

A more recent and more directly targeted approach has been use of selective PI3K γ inhibitors. Idelalisib (previously named GS-1101) led to reduced mutant PI3K γ activity in vitro and was subsequently used in a clinical trial. Oral administration of the drug in 6 APDS patients over 12 weeks led to normalization of numbers of circulating B cells and T cells, and significant reduction of lymphoproliferative manifestations of the disease (73). Two phase II clinical trials are currently evaluating the use of first PI3K γ inhibitors in APDS.

Whim syndrome and plerixafor

The warts, hypogammaglobulinemia, infections, myelokathexis (WHIM) syndrome is a rare primary immunodeficiency caused, in most cases, by autosomal dominant GOF mutations in the CXCR4 gene (74). WHIM syndrome presents with recurrent bacterial infections, neutropenia secondary to bone marrow retention, warts, and malignancies including EBV-driven B cell lymphomas, T-cell lymphomas and HPV induced carcinomas (74).

The CXCR4 gene codes for the CX chemokine receptor 4 (CXCR4), a 352 amino acid seven transmembrane domain G protein-coupled receptor that is ubiquitously expressed by hematopoietic cells. CXCR4 selectively binds the chemokine CXCL12, also named stromal cell-derived factor 1 (SDF1), produced by bone marrow stromal cells, spleen red pulp and lymph node medulla. The CXCR4-CXCL12 interaction plays a crucial role in regulating bone marrow homeostasis and cell trafficking (75, 76). Pathogenic mutations in CXCR4 causing WHIM syndrome cluster in the region coding for

the cytoplasmic tail of the receptor (77) and lead to defective ligand mediated receptor internalization (78) and defective retention of mature leukocytes in the bone marrow (79).

Targeted therapies for patients with WHIM syndrome and GOF mutations in CXCR4 are currently undergoing evaluation. The small molecule CXCR4 antagonist plerixafor is FDA approved for stem cell mobilization for autologous transplantation after cytoreductive therapy in patients with non-Hodgkin lymphoma or multiple myeloma (80). In vitro studies in cells transfected with the most common CXCR4 variant causing WHIM syndrome (CXCR4R334X) and leukocytes from a WHIM patient, show that plerixafor acts as an antagonist for the mutant receptor with equivalent efficacy to wild type CXCR4 (81). A phase I trial of plerixafor as a treatment for WHIM syndrome was published in 2011 and reported dose-dependent increases in lymphocyte, monocyte and neutrophil blood counts without significant side effects (82). A subsequent trial in three patients that received plerixafor for 19-52 months showed that prolonged use of the medication was safe and ameliorated leukopenia, wart burden, frequency of infections and improved quality of life. One patient demonstrated stabilization of HPV-associated oropharyngeal squamous-cell carcinoma (83). Increased total white cell counts in WHIM patients treated with plerixafor are mostly due to lymphocytes (82). Responding lymphocytes are mostly of T cell and B cell lineage and exhibit significant variation after each dose (83). Although neutrophils are less responsive to plerixafor in these patients, treated individuals exceed an absolute neutrophil count of 500 cells/ μ L and experience sustained responses between doses (82, 83).

Cytokine blockade

Cytokines serve as intercellular messengers in host defense, tissue repair, and remodeling. They also are responsible for the pathogenesis of many autoimmune and autoinflammatory diseases. Over 20 years ago, cytokine blockade began revolutioniz-

Archive of SID

ing treatment of common disorders such as inflammatory bowel disease, and rheumatoid arthritis. While the number of cytokines for which blockade is available continues to increase, older mainstays have proven to be particularly powerful tools in treatment of newly identified monogenic disorders. Key examples are discussed below.

TNF- α and Deficiency of adenosine deaminase 2

Deficiency of adenosine deaminase 2 (DADA2) is a vasculitis syndrome caused by biallelic mutations in the adenosine deaminase 2 gene (ADA2). The disorder has a pleiotropic presentation that can include livedo reticularis, polyarteritis nodosa, hypogammaglobulinemia, neutropenia, and pure red cell aplasia (PRCA). The most devastating manifestation of the disease is a high incidence of risk of life-threatening ischemic and/or hemorrhagic stroke (84, 85).

ADA2, like its homolog ADA1, has enzymatic activity that acts in conversion of adenosine to inosine and 2'-deoxyadenosine to 2'-deoxyinosine (86). However, the two enzymes, while partially homologous, have distinct structures and tissue distribution which leads to dramatically different functions. While ADA1 is expressed in all cell types, ADA2 expression is restricted to myeloid cells (86). ADA2 plays an important role in monocyte proliferation and macrophage differentiation - monocytes derived from patients with DADA2 favor differentiation to proinflammatory M1 macrophages rather than anti-inflammatory M2 macrophages (84).

Increased production of TNF- α is likely to contribute to pathogenesis of the vasculitis component of the disease as TNF α inhibitors have been used successfully to control fevers, vasculopathy and dramatically reduce the risk of stroke. In a multicenter series of patients with this disease, 10 patients received anti-TNF treatment and 9 had clinical improvement indicative of complete remission. The 10th patient remained steroid dependent

(87). In another study of 15 patients with DADA2 with a history of stroke, ant-TNF therapy showed impressive results (88). Before the initiation of anti-TNF therapy, the patients had a total of 55 strokes during 2077 cumulative patient-months (10 of these patients had tried other forms of immune modulation during this time unsuccessfully). After therapy, the patients had no strokes during 733 cumulative patient-months. 37 strokes that would have been expected using a binomial approach for matched follow-up time.

IL-1 blockade for treatment of cryopyrin-associated periodic syndromes

Activating mutations in NLRP3 have been defined as the molecular mechanism for what were previously characterized as three phenotypically distinct disorders: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease (NOMID). These disorders are now recognized as part of a spectrum of disease now referred to as cryopyrin-associated periodic syndromes (CAPS) (89, 90). Point mutations in NLRP3 lead to the inappropriate production of active IL-1 β by disrupting defective self-inhibition or through resistance to negative regulatory signals (91, 92).

Patients with FCAS have the mildest form of the disease and present with cold-induced neutrophilic urticaria, fever, and arthralgias reminiscent of familial Mediterranean fever. Patients with the Muckle-Wells phenotype have these symptoms more easily triggered, and additionally suffer from progressive hearing loss as well as kidney disease due to secondary amyloidosis. Children with NOMID, the most severe form of the disease, suffer from severe full-body rashes, joint destruction, and chronic sterile meningitis (89, 90).

The central role for IL-1 β in disease pathogenesis is demonstrated through the efficacy of anti-IL-1 directed therapies (93). Two randomized double-blind placebo-controlled trials on the efficacy of IL-1 blockade on treatment of CAPS have been performed. Riloncept, a dimeric fusion protein

that consists of the ligand-binding domain of IL1-R1

Archive of SID

and IL-1 receptor accessory protein binds and neutralizes IL-1. Compared to placebo, riloncept was superior in controlling symptoms in 47 patients with MWS or FCAS (94). In another study, canakinumab, a human monoclonal antibody targeted at IL-1 β led to complete response during the open-label phase of a study that included 35 MWS patient and 4 NOMID patients. During the subsequent randomized phase of the study, all patients in the drug group remained in remission while 81% of the patients in the placebo group had a relapse of symptoms (95). Remarkably, patients with NOMID have demonstrated reversal of the neurological manifestations of disease including chronic aseptic meningitis, papilledema, and hearing loss secondary to cochlear inflammation (96).

IL-12/IL-23 blockade in Leukocyte adhesion deficiency

Leukocyte adhesion deficiency type 1 (LAD-1) is an autosomal recessive disorder caused by biallelic mutations in in ITGB2, the gene that encodes integrin beta chain-2, also known as CD18. Patients with this disorder present with delayed umbilical cord separation and recurrent life-threatening bacterial infections. This is due to impaired leukocyte adhesion to activated endothelium which prevents leukocyte migration from the blood to sites of infection and injury (97). Patients who survive infancy frequently suffer from severe periodontitis and tooth loss. This had been long-presumed to be due to a role for neutrophils in preventing and clearing periodontal infection. However, recent findings suggest that this process is due excessive production of IL-17 in the periodontal tissue (98). Moutsopoulos et al. thus hypothesized that of ustekinumab, an IL-12/IL-23 antagonist approved for treatment of psoriasis and Crohn's disease would be an effective treatment for these LAD-1 manifestation through targeting the IL-17/IL-23 pathway (99). The therapy was trialed in a 19 year-old patient with severe periodontitis and a chronic sacral wound. Within weeks of starting treatment, the patient had a dramatic response, with substantial reduction of oral

lesions. The patient's sacral wound also demonstrated an impressive response to therapy with progressive healing over a course of about 10 months. This treatment strategy is now in clinical trials to demonstrate efficacy in a larger patient cohort.

Conclusions

While precision medicine has been part of clinical immunology since the earliest days of the field, it has been fewer than 20 years since the completion of the human genome project fully set the stage for widespread use of targeted therapies. In many cases, precision medicine offers faster and more complete responses with fewer side effects than conventional therapies. There is great promise for the future as new molecular pathways are defined and novel therapeutics are developed to target an increasing number of these pathways.

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