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Targeted Therapies for PIDs

IDFA Immune Deficiencies Foundation Australia

IPOPI INTERNATIONAL PATIENT ORGANISATION FOR PRIMARY IMMUNODEFICIENCIES

ABBREVIATIONS

CANDLE	Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature
CAPS	Cryopyrin-associated periodic syndromes
DIRA	Deficiency of the IL-1 receptor antagonist
FCAS	Familial cold autoinflammatory syndrome
GOF	Gain-of-function
Ig	Immunoglobulin
IL	Interleukin
JAK	Janus kinase
mAb	Monoclonal antibody
LRBA	Lipopolysaccharide-responsive and beige-like anchor protein
mTOR	Mammalian target of rapamycin
MWS	Muckle-Wells syndrome
PID	Primary immunodeficiency
POMP	Proteasome maturation protein

Targeted therapies for PIDs (1st edition)

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INTRODUCTION

This booklet explains how targeted therapy with biological agents or small molecule drugs might be used to treat PIDs.

Primary immunodeficiencies (PIDs) are a group of rare diseases that occur when some components (mainly cells and/or proteins) of the immune system do not work properly. People with PIDs are more susceptible to, and less able to fight, infections and require life-long management to support their immune system. They may also have changes in the way their immune system work making them susceptible to autoimmune and autoinflammatory diseases, or severe allergies and malignancies. When this is not possible to cure them, the aim of treatment for patients with PIDs is to control the disease and to prevent or treat infections through anti-infectious prophylaxis and/or immunoglobulin (Ig) replacement therapy. More recently, new targeted therapies have been developed for the treatment of PIDs including biological agents and small molecule drugs. The following sections explain what targeted therapies are and for which PIDs these agents might be used.

WHAT ARE TARGETED THERAPIES?

As the understanding of the immunobiology underlying the pathophysiology of immune dysregulation has evolved, the ability to precisely identify the molecular basis of immunological disorders has greatly increased, paving the way for the application of targeted therapies. Some targeted therapies specifically target molecular components of the immune system; for example, altering the expression of a specific gene or changing the activity of a specific protein or cell type. In doing so these targeted therapies inhibit, enhance or restore the balance of the specific component(s) of the immune system that are not functioning properly in a given PID. Targeted therapies also include biological agents and small molecule drugs that target specific genes or proteins or components of the immune system. These therapies could be modified antibodies, often referred to as monoclonal antibodies, or chemicals such as cytokines. Monoclonal antibodies are becoming an increasingly common type of biological therapy for many different cancers and other conditions.

WHY MIGHT THESE ADVANCED TECHNOLOGIES BE USEFUL?

In the last decade, huge advances in the knowledge of genetics and understanding of the underlying pathophysiology of PIDs, together with how changes in certain molecules generate alterations in important immune system pathways, has created new opportunities for the more precise treatment of patients. This greater understanding of the immune system function allows a deeper comprehension of changes in its regulation and the impact on patients, who often cannot be categorised as a specific PID or particular autoimmune disease. These therapies provide an opportunity to address the specific immune system defects that are associated with individual PIDs. This is sometimes referred to as precision medicine or personalised medicine.

WHICH PIDS MIGHT BENEFIT FROM TARGETED THERAPIES?

Targeted therapy appears to be most beneficial for the treatment of patients with clinical manifestations of immune dysregulation and hyperinflammation, but it may not be suitable for all PIDs or all patients. Various targeted therapies and their potential PID indications are summarised in Table 1. As with all treatments, these agents are associated with side effects, which may include an increased risk of serious infection. For example, anti-TNF agents increase the risk of tuberculosis, especially in patients receiving other immunosuppressive agents such as corticosteroids, and the targeted therapy ruxolitinib can lead to Herpes Simplex Virus inflections.

TABLE 1

TARGETED THERAPIES AND THEIR MOLECULAR TARGETS [1]

Targeted therapy	Molecular structure	Molecular target	Potential PID indications
Biological agents			
Abatacept Belatacept	CTLA-4 IgG fusion protein	B7-1 (CD80), B7-2 (CD86)	CTLA-4 haploinsufficiency, LRBA deficiency
Anakinra	Recombinant human IL-1R antagonist	IL-1R	Cryopyrin-associated periodic fever syndromes
Canakinumab	Antihuman IL-1 IgG1 mAb	IL-1β	CAPS, FCAS
Rilonacept	IgG1 linked to IL-1R and IL-1R accessory protein		MWS, DIRA
Etanercept	Fusion protein	TNF-α	SAV1 CANDLE syndrome POMP deficiency
Infliximab	Chimeric mAb		
Adalimumab	Humanized mAb		
Tocilizumab	IgG1k recombinant humanized mAb	IL-6R	STAT3-GOF

[1] Delmonte OM, Notarangelo LD. Targeted therapy with biological and small molecules in primary immunodeficiencies. Med Princ Pract 2020;29:101–12.

TARGETED THERAPIES AND THEIR MOLECULAR TARGETS [1]

Small molecule drugs			
Sirolimus	Macrolide compound	mTOR	NLCR4-GOF POMP deficiency CTLA-4 haploinsufficiency APDS
Ruxolitinib Baricitinib	Pyrazole molecules	JAK1, JAK2, JAK3	STAT3-GOF* STAT1-GOF CANDLE syndrome APDS
Tofacitinib	Pyrrolopyrimidine		
Leniolisib	Pyrrolopyrimidine	PI3K-delta inhibitor	
Tadekinig-α	Recombinant IL-18 binding protein	IL-18 binding protein	NLCR4-GOF

*Only ruxolitinib and tofacitinib.

APDS, activated phosphoinositide 3-kinase delta syndrome; CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; CAPS, cryopyrin-associated periodic syndromes; DIRA, deficiency of the IL-1 receptor antagonist; FCAS, familial cold autoinflammatory syndrome; GOF, gain-of-function; Ig, immunoglobulin; IL, interleukin; JAK, Janus kinase; LRBA, lipopolysaccharide-responsive and beige-like anchor protein; mAb, monoclonal antibody; mTOR, mammalian target of rapamycin MWS, Muckle-Wells syndrome; POMP, proteasome maturation protein.

As an example of targeted therapy, CTLA4 is a protein that inhibits excessive immune responses, so reduced CTLA4 can result in increased autoimmunity. Patients with CTLA-4 deficiency develop multi-organ autoimmune manifestations including cytopenia, inflammatory bowel disease, psoriasis and thyroid disease. The biological therapy abatacept can restore CTLA4 immune inhibition and suppress autoimmunity. [2]

STAT3 gain of function mutations are associated with early onset autoimmunity, marked short stature and hypogammaglobulinaemia. IL-6 is a key cytokine that activates the STAT3 signaling pathway so blocking this with tocilizumab, an anti-IL-6R monoclonal antibody, inhibits STAT3 activity and reduces autoimmune symptoms. [3]

AVAILABILITY OF TARGETED THERAPIES

An increasing number of targeted therapies are under evaluation based on accumulating experiences reported in the medical literature (single case reports and case series) for the management of a number of PIDs. Before these agents can be considered as routine treatment options, many questions remain regarding the choice of drug for the different PIDs, the appropriate dose (especially in children), the efficacy in terms of alleviating the various manifestations of PIDs, the monitoring of treatment, and the management of potential side effects particularly in patients susceptible to infection. [4]

[2] Lee S et al. Abatacept alleviates severe autoimmune symptoms in a patient carrying a de novo variant in CTLA-4. J Allergy Clin Immunol 2016; 137: 327–30.

[3] Khoury T et al. Tocilizumab Promotes Regulatory T-cell Alleviation in STAT3 Gain-of-function-associated Multi-organ Autoimmune Syndrome. Clin Ther 2017; 39: 444–9.

[4] Hadjadj J, Frémond M-L, Neven B. Emerging Place of JAK Inhibitors in the Treatment of Inborn Errors of Immunity. Front Immunol 2021 Sep 17;12:717388. doi: 10.3389/fimmu.2021.717388.

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Other booklets are available in this series.

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