Trends in Immunotherapy (2024) Volume 8 Issue 1
doi: 10.24294/ti.v8.i1.4562

REVIEW ARTICLE

IFN-γ auto-antibody: An overview as one of the autoimmunity effect

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ABSTRACT

Interferon Gamma (IFN-γ) plays a vital role in normal immune surveillance and possesses immunomodulatory, antimicrobial, and anticancer properties. It stands as the exclusive type II IFN, and its production is regulated by cytokines released by Antigen-Presenting Cells (APCs), particularly interleukin (IL)-12 and IL-18. These cytokines act as a connecting link between infection and IFN-γ production in the innate immune response. The functional IFN-γ receptor (IFNGR) consists of two ligand-binding IFNGR1 chains and two signal-transducing IFNGR2 chains, along with associated signaling machinery. Both IFNGR1 and IFNGR2 chains belong to the class II cytokine receptor family, characterized by ligand binding in the small angle of a V formed by the two Ig-like folds in the extracellular domain. Autoantibodies targeting interferon-gamma (IFN-γ) can lead to immunodeficiency and are linked to various opportunistic infections. The immunopathogenesis is associated with the neutralizing activity of these autoantibodies on the IFN-γ signaling pathway, resulting in the blocking of certain immune responses activated by IFN-γ. This review provides a concise overview of IFN-γ Autoantibody detection, the immunopathogenesis of related diseases, and potential treatment options.

Keywords: interferon gamma; autoantibody; detection; immunopathogenesis; treatment

ARTICLE INFO

Received: 6 February 2024
Accepted: 3 May 2024
Available online: 28 May 2024

1. Introduction

Interferon (IFN)-γ, the sole member of the Interferon family that functions as an immunomodulator with antimicrobial and anticancer properties[1], distinguishes itself from type I IFNs by binding to a different receptor and having a distinct chromosomal locus[2]. Initially, it was believed that IFN-γ was exclusively produced by CD4+ T helper cell type 1 (Th1) lymphocytes, CD8+ cytotoxic lymphocytes, and NK cells[2,3]. However, there is no evidence supporting the exclusive secretion by these cell types, as other cells like B cells, NKT cells, and professional antigen-presenting cells (APCs) may also release IFN-γ, as discussed in various reviews[4–6].

Professional APCs, such as monocytes/macrophages and dendritic cells (DCs), acting locally, play a significant role in activating nearby cells and self-activation[5,7].

In early host defense against infection, NK cells and possibly professional APCs are likely sources of IFN-γ, while T lymphocytes become the primary contributors in the adaptive immune response[5,8]. IFN-γ, contributing to immune surveillance, has diverse effects, including the induction of MHC-associated antigen presentation pathways, development of Th1 responses, antimicrobial activities, stimulation of anticancer activities, modulation of leukocyte trafficking, and facilitation of inflammation[9,10]. In antibacterial actions, IFN-γ acts as a macrophage activator, enhancing microbicidal effects through receptor-mediated phagocytosis to support innate defense[9,11].

Autoantibodies (Aabs) targeting interferon-gamma (IFN-γ) are associated with multiple opportunistic infections and can potentially induce immunodeficiency[12]. The immunopathogenesis is linked to the neutralizing action of these autoantibodies on the IFN-γ signaling pathway, resulting in the inhibition of certain immune responses triggered by IFN-γ[1,4].

When anti-interferon (IFN)-α AAbs were found in adults with multiple opportunistic infections, similar to what was seen in patients with advanced HIV infection, the phrase “adult-onset immunodeficiency” was first used by Browne et al. to describe this type of immunodeficiency syndrome. Anti-IFN-α AAbs have been shown in cumulative studies to be a direct cause of immunodeficiency associated with intracellular infections, primarily in adults[11].

Instead of being the outcome of opportunistic infections, immunodeficiency is thought to be caused by anti-IFN-AAbs. Activated T cells, natural killer (NK) cells, and macrophages release interferon-gamma (IFN-α), a major immune regulator essential for managing intracellular infections. When homodimer IFN-α binds to its receptor, the Janus-activated kinase (JAK)-STAT pathway is triggered. The JAK-STAT signal controls different biological responses and balances the transcriptional activation of many genes[13]. Anti-IFN-αAAbs with high titers can prevent IFN-α from binding to its receptor, hence blocking the first steps of IFN-α signal transduction, such as STAT-1 phosphorylation or STAT-1 protein production. Additionally, these autoantibodies prevent the up-regulation of tumor necrosis factor[TNF]-α, and interleukin (IL)-12 production, which is one of the physiologic downstream effects of IFN- binding[1,14].

Purified anti-IFN-α AAbs have the ability to prevent peripheral blood mononuclear cells from expressing HLA class II and from inducing IFN-α-inducible genes[15]. Furthermore, individuals with positive anti-IFN-α AAbs could inhibit macrophage and monocyte IFN-α-mediated antimicrobial immunity. These comprise the formation of cytokines, chemokines, and inducible nitric oxide (iNO)/nitric oxide (NO), biosynthesis and reactive oxygen species (ROS) generation, phagocytosis and degradation effectiveness, and IFNγ-driven polarization and M1 macrophage activation[1,14]. These data unequivocally show that neutralizing anti-IFN-α AAbs can block IFN-ε binding to its receptor, preventing downstream signal transduction and hence impairing immune responses against intracellular infections.

This review discusses our current understanding of anti-IFN-γ AAbs in terms of Immunodeficiency affected by the AAbs, related diseases and its potential treatment.

2. Interferon-gamma (IFN-γ)

Interferon is a natural protein from the human immune system that functions to fight disease-causing (pathogens), such as bacteria, viruses, and cancer cells in the body. Almost every cell of the body produces interferon, which consists of 3 main types, namely α, β and γ. Body cells that are infected with viruses or bacteria will secrete interferon α and β as a warning signal to the immune system. This triggers white blood cells to release interferon γ to fight viruses or bacteria.

Interferon (IFN) belongs to a large family of cytokines, divided into two types based on structure, function, and stimulus: (i) type I IFN, responding to viral infections, further classified into several classes such as IFN-α, -β, -ε, -κ, -ω, -δ, and -τ; (ii) type II IFN, known as IFN-γ, secreted by cells stimulated by various inflammatory stimuli and other immune reactions.

The production of IFN-γ is regulated by cytokines released by Antigen-Presenting Cells (APCs), particularly interleukin (IL)-12 and IL-18, serving as a bridge connecting infection to IFN-γ production in the innate immune response[10].

The functional IFN-γ receptor (IFNGR) consists of two ligand-binding IFNGR1 chains and two signal-transducing IFNGR2 chains, along with associated signaling machinery. Both IFNGR1 and IFNGR2 chains belong to the class II cytokine receptor family, characterized by ligand binding in the small angle of a V formed by the two Ig-like folds in the extracellular domain[16].

Beyond its role in host defense, IFN-γ may contribute to autoimmune pathology. While IFN-γ production has been shown to limit diseases in certain autoimmune models, such as murine experimental allergic encephalomyelitis (EAE)[17], it may contribute to autoimmune nephritis[18]. In humans, IFN-γ is implicated in the pathology of diseases like systemic lupus erythematosus[19], multiple sclerosis[20], and insulin-dependent diabetes mellitus[15].

IFN-γ primarily utilizes the Jak-Stat pathway, a signaling pathway employed by more than 50 cytokines, growth factors, and hormones to modulate gene regulation[21]. The Jak-Stat signaling cascade involves a series of events, including the sequential recruitment and activation of Janus family kinases (Jaks: Jaks 1–3 and Tyk2) and the Signal Transducers and Activators of Transcription (Stats 1–6, which includes Stats5a and Stats5b). This orchestrated process controls the transcription of target genes through specific response elements

The significance of IFN-γ lies in its ability to synergize or antagonize the effects of cytokines, growth factors, and pathogen-associated molecular pattern (PAMP)-signaling pathways, which holds particular importance in macrophage biology. Macrophages receive a multitude of signals continuously and must integrate them to produce a response appropriate to the extracellular environment. This ability to interact with various signaling pathways underscores the versatile role of IFN-γ in influencing macrophage responses.

3. Interferon-gamma autoantibody

Interferon-γ (IFN-γ), derived from a single gene located on chromosome 12 in humans and chromosome 10 in mice, is a glycosylated protein consisting of 143 amino acids. It shares slight sequence homology with the IFN-α and IFN-β classes but exhibits a broader range of activities, positioning it as a modulator of the immune system in addition to sharing biological activities with type I IFN[11,12,15–21].

IFN-γ is predominantly produced endogenously by activated T lymphocytes (CD4+ and CD8+) and Natural Killer (NK) cells in response to specific antigenic stimuli. As a hallmark cytokine of the TH1 subset, IFN-γ plays a crucial role in macrophage activation and contributes significantly to cell-mediated immunity against intracellular microbes[22–25].

In the context of tuberculosis, IFN-γ, a cytokine associated with Th-1 cells, is crucial in the efforts to eliminate Mycobacterium tuberculosis and respond to other intracellular bacteria. Levels of IFN-γ are elevated in the sputum and serum of tuberculosis patients at the onset of diagnosis and treatment, gradually decreasing following anti-tuberculosis therapy[10–12,17–18].

The production of IFN-γ through CD4+ T cells involves two pathways: the T cell receptor (TCR)-mediated antigen-dependent pathway, which is sensitive to cyclosporine, and the cytokine-induced, cyclosporine-insensitive pathway. Experimental induction of IFN-γ production can also be achieved by stimuli mimicking TCR activation, such as mitogens (e.g., concanavalin A or phytohemagglutinin), cross-linking

antibodies, or pharmacological agents (e.g., a combination of phorbol myristate acetate and calcium ionophore)[23–26].

In inactive (resting) T cells, the IFN-γ gene remains unexpressed, and consequently, the protein is not detectable. However, upon T cell activation, IFN-γ becomes detectable within 6–8 h, reaching its peak level in 12–24 h, followed by a subsequent decrease until it returns to baseline values. Both TH1 and CD8+ cells, having undergone prior differentiation, exhibit robust secretion of IFN-γ in response to stimulation from a combination of IL-12 and IL-18 (also known as IFN-inducing factor, IGIF), without the necessity for stimulation via the T cell receptor (TCR)[14,19]. Notably, the duration of IFN-γ production triggered by cytokine stimulation was significantly longer than that resulting from TCR stimulation.

The synergy between IL-12 and IL-18 induces IFN-γ through a mechanism involving the transcription factors Stat4 and NF-κB. IFN-γ plays a role in downregulating IL-4 and IL-10 production by TH2 cells. During the early priming of T cells, the presence of IFN-γ can enhance the polarization of TH2 cells and IL-4-producing cells. Moreover, IFN-γ exerts control over the production and activation of T cells, particularly CD4+/CD25+ regulatory T cells (Tregs). Tregs contribute to the induction of various immune responses and the establishment of immune tolerance[26–35].

Cell-mediated immunity consists of two main types of reactions: CD4+ T cells recruit phagocytic cells and activate them through CD40 and IFN-γ ligands. This activation results in the killing of phagocytosed microbes. Additionally, CD8+ cytotoxic T lymphocytes play a crucial role in killing infected host cells. IFN-γ is central to these processes as it activates signaling pathways and transcription factors, with STAT1 being particularly important. Simultaneously, Toll-like receptor (TLR) and CD40 signals activate the transcription factor NF-κB and activate protein 1 (AP-1). These transcription factors stimulate the expression of various enzymes in macrophage phagolysosomes, including phagocytic oxidase enzymes, inducible nitric oxide synthase (iNOS), and lysosomal enzymes. These substances contribute to the destruction of ingested microbes within vesicles, constituting the microbicidal action by activated macrophages[26–35].

IFN-γ also stimulates the production of antibody isotypes, such as IgG2a in mice, which activate complement and opsonize bacteria for phagocytosis, enhancing the effector function of macrophages[10,11].

Furthermore, IFN-γ induces autophagy in cells infected with mycobacteria, and this induction is associated with protective immunity against tuberculosis. However, IL-6 produced by mycobacterial-infected macrophages inhibits the macrophage response to IFN-γ[10–12,16–19].

Anti-interferon-gamma (IFN-γ) autoantibodies are increasingly recognized as a cause of adult-onset immune deficiency (AOID) worldwide. Individuals with AOID are susceptible to various intracellular pathogens, particularly non-tuberculous mycobacteria, and most of these patients experience a refractory clinical course[22,23].

A swift decrease in anti-IFN antibody titers within the first 6 months of immunosuppressive treatment is indicative of a favorable outcome. However, when encountering cases with persistently high titers of anti-IFN antibodies despite treatment with intravenous cyclophosphamide (IVCY), rather than being widespread, clinicians should consider transitioning to another immunosuppressive drug with a distinct target of action. This approach aims to mitigate the risk of infections associated with the prolonged use of cyclophosphamide. Opting for less toxic immunosuppressive drugs may produce better results and contribute to the overall management of the patient's condition[22–27,30,31,36–38].

IFNγ operates directly on brain cells in addition to these other roles[39–44]. For instance, IFNγ causes the non-cytolytic removal of certain neurotropic viruses from Central Nervous System (CNS) neurons, including the measles and Sindbis viruses[39,40,45]. However, in many CNS disorders, IFNγ also contributes to neurodegeneration[46–48]. Consequently, it is still unknown exactly what part IFNγ plays in CNS inflammation,

but it most likely involves a complicated cascade of reactions from several cell types.

There is evidence that IFNγ has both harmful and beneficial effects in Alzheimer's disease (AD). When co-stimulated with IFNγ and TNFα or IL-1β, astrocytes—the primary source of Aβ in the brain—are driven to generate Aβ peptides[49]. In human astrocytes, IFNγ alone can increase the production of β-secretase, indicating that IFNγ may improve the processing of Aβ[50]. Compared to cells from healthy controls or mild AD patients, mononuclear cells from individuals with moderately severe AD produce higher amounts of IFNγ[51,52]. Furthermore, primary neurons treated with Aβ peptides die more frequently when exposed to IFNγ[53].

While there is conflicting evidence from human research about the presence of enhanced IFNγ in the AD brain, polymorphisms in the IFNγ promoter that result in high IFNγ expression are linked to a slower rate of AD progression[54]. These results imply that diverse impacts of the neuroinflammatory response, including IFNγ production, on brain cells may occur during the development of AD.

IFNγ is present in MS lesions and is a component of the inflammatory milieu in MS patients[55,56]. During intravenous administration, early clinical trials of recombinant IFNγ treatment increased many inflammatory markers and worsened symptoms of multiple sclerosis[57]. Prior to clinical attacks, serum levels of IFNγ also rise, while IFNα expression rises during remissions[58]. IFNγ has been linked to MS, although there are still many unanswered concerns regarding how it plays a part in the disease's pathophysiology. The majority of in vivo research has concentrated on how IFNγ affects mature oligodendrocytes and peripheral immune cells; its impact on NSPCs in the development and course of MS and Experimental Autoimmune Encephalitis [EAE] is less well understood.

Numerous investigations reveal that IFNγ activates macrophages and microglia, upregulates MHC molecules, and induces inflammatory mediators, all of which lead to the death of oligodendrocytes (reviewed by Goverman[59]. Research conducted on transgenic mice that exhibit temporally regulated IFNγ expression reveals that the length of time IFNγ is expressed determines whether it has a positive or negative impact on the development of EAE[60,61]. Prior to the commencement of EAE, IFNγ production in the CNS slows down the disease's progression and stops oligodendrocyte loss, demyelination, and axon degeneration. Pancreatic endoplasmic stress kinase (PERK) activation in oligodendrocytes mediates this protective impact of IFNγ[61].

According to additional research, increased PERK signaling prevents oligodendrocyte death prior to the onset of clinical disease and obstructs axonal degeneration and demyelination brought on by EAE at the worst stage of the illness.106. The preservation of myelin integrity may be the cause of these protective effects on axons rather than a reduction in the inflammatory response. Nuclear factor kappa-B, an antiapoptotic transcription factor that may serve as an oligodendrocyte defense mechanism, is activated by PERK signaling[62]. On the other hand, lesion remyelination and oligodendrocyte regeneration are inhibited by IFNγ expression during the recovery stage of EAE.104. Nevertheless, in the chronic inflammatory milieu of multiple sclerosis, the effects of IFNγ on NSPC activity and their possible development into oligodendrocyte precursors are still mainly unknown.

In addition, IFNγ plays a vital role in preventing the transmission of numerous neurotropic viruses, such as the Sindbis virus, herpes simplex virus, Theiler's virus, and measles virus[42,63–65]. IFNγ has well-established antiviral and immunomodulatory functions, although it is unclear how it influences NSPC activity when viral infections are present. IFN-γ autoantibody production is thought to inhibit the function of IFN-γ in the above disease pathogenesis.

4. Adult-onset immunodeficiency syndrome

4.1. Adult-onset immunodeficiency in Thailand and Taiwan

Autoantibodies against interferon-γ (IFN-γ) are linked to severe disseminated opportunistic infections,

although their importance and prevalence are not well understood. An extensive study involving HIV-uninfected Taiwanese adults with opportunistic infections, without previously identified immunodeficiency, was conducted in Thailand. The absence of familial clustering and the late onset of the disease argued against a monogenic cause. Lymphocytes, including CD4+ T cells, and other hematopoietic elements appeared essentially normal in number and surface-receptor distribution, including the interferon-γ receptor 1. Notably, while levels of several anti-cytokine autoantibodies varied significantly between groups, only anti–interferon-γ autoantibodies distinguished patients with opportunistic infections, and specifically, anti–interferon-γ IgG inhibited interferon-γ–dependent STAT1 phosphorylation[10].

In contrast to patients with advanced HIV infection, individuals in this study were highly susceptible to rapidly growing mycobacteria[66]. Complete interferon-γ–receptor deficiency makes individuals susceptible to rapidly growing mycobacteria, whereas partial receptor defects do not[67].

This study establishes a strong association between adult-onset immunodeficiency syndrome and high-titer neutralizing antibodies to interferon-γ, emphasizing the crucial role of interferon-γ in controlling numerous pathogens. The observation that many patients with anti–interferon-γ autoantibodies remain actively infected despite antimicrobial therapy suggests that investigating therapeutic targeting of these autoantibodies may be warranted[10,68].

4.2. Autoantibody to interferon-gamma associated with adult-onset immunodeficiency in Non-HIV individuals in northern Thailand

Autoantibodies against interferon-gamma (IFN-ɣ) have been reported to be associated with adult-onset immunodeficiency in patients from Asian countries. This study aimed to determine the prevalence of autoantibodies to IFN-ɣ among non-HIV patients in northern Thailand who were repeatedly infected with unusual intracellular pathogens[69].

This study, the first report from northern Thailand, reveals an increasing number of non-HIV-infected patients with adult-onset immunodeficiency in the Asian population. Retrospective data collection from 109 patients suspected of having adult-onset immunodeficiency at Chiang Mai University Hospital between 1991 and 2011 indicated that this newly recognized syndrome was slightly more common in females, with a mean age at the time of first diagnosis of 49 years. These patients exhibited a relatively high mortality rate, with 32% dying at a median time of 25 months after diagnosis. Although there has been no longitudinal study to compare survival rates, other observations have also noted a poor prognosis in patients with adult-onset immunodeficiency[70].

This study provides further evidence that autoantibodies to IFN-ɣ may play a crucial role in cell-mediated immunity defects among non-HIV-infected Thai patients in northern Thailand experiencing repeated episodes of unusual intracellular infections. Using the cutoff optical density at the 99th percentile of HIV-infected and healthy controls, all cases in this study tested positive for autoantibodies to IFN-ɣ. In contrast, neither HIV-infected controls, many of whom had a history of similar opportunistic infections, nor healthy controls had IFN-ɣ autoantibodies[71].

Subsequent research revealed that serum from patients with opportunistic infections who were HIV-negative and did not have tuberculosis prevented IFN-γ-activated STAT1 activation and IRF1 transactivation. Moreover, the synthesis of chemokines, cytokines, and inflammation that is regulated by IFN-γ was also inhibited. Based on IFN-γ's role as a proinflammatory activator of innate immunity and an activator of macrophage development, it is proposed that the autoAbs found in NTM patient serum block IFN-γ, hence controlling macrophage antimicrobial activity. IFN-γ-induced type 1 macrophage (M1) development in PMA-stimulated human monocytic THP-1 cells was suppressed in the presence of patient serum. Proinflammatory variables, such as cytokines/chemokines and reactive oxygen/nitrogen species, were dramatically inhibited by treatment with patient serum by M1 macrophages. Significantly, cotreatment with patient serum reduced the

amount of heat-killed mycobacterium and enhanced phagocytosis by IFN-γ[1,14].

The study conducted in northern Thailand aimed to determine the prevalence of autoantibody to interferon-gamma (IFN-γ) among non-HIV patients repeatedly infected with unusual intracellular pathogens. It revealed that adult-onset immunodeficiency is on the rise in the Asian population, particularly among non-HIV-infected individuals. Retrospective data from 109 patients suspected of having adult-onset immunodeficiency at Chiang Mai University Hospital between 1991 and 2011 indicated that this newly recognized syndrome is slightly more common in females, with a mean age at the time of the first diagnosis being 49 years. The patients had a relatively high mortality rate, with 32% succumbing at a median time of 25 months after diagnosis. Although there was no longitudinal study for survival rates, poor prognosis was observed, aligning with findings from Tang et al.[69].

Further evidence was found supporting the role of autoantibody to IFN-γ in cell-mediated immunity defects among non-HIV-infected Thai patients in northern Thailand experiencing repeated episodes of unusual intracellular infections. Using a cutoff optical density at the 99th percentile of HIV-infected and healthy controls, all cases in the study tested positive for autoantibody to IFN-γ, while neither HIV-infected controls, many of whom had a history of similar opportunistic infections, nor healthy controls exhibited the IFN-γ autoantibody[67].

A subgroup analysis comparing clinical characteristics and laboratory findings between cases with and without active opportunistic infection at study entry revealed correlations with disease activity, including higher white blood cell count and absolute neutrophil count, along with a lower hemoglobin level. Interestingly, patients with active infections showed relatively higher levels of autoantibody to IFN-γ compared to those without active infections[69].

In conclusion, the study confirmed a strong association between adult-onset immunodeficiency and the presence of autoantibody to IFN-γ in non-HIV individuals in northern Thailand. The elevated levels of the antibody in patients with active opportunistic infections further suggest its potential role in disease activity[69].

Diagnosing adult-onset immunodeficiency can be difficult, especially when HIV infection is not present. Aabs against IFN-γ have been linked to a number of opportunistic illnesses. The most prevalent infectious disease is diffused nontuberculous mycobacterial (NTM) infection, however other common opportunistic pathogens seen in this patient population include *Salmonella species*, *Varicella-zoster virus*, *Histoplasma capsulatum*, *Burkholderia pseudomallei*, *Talaromyces marneffei*, and *Cryptococcus neoformans*[39,62,64,70]. Concurrent infections involving a minimum of two opportunistic pathogens are a more precise indicator of the impaired immune status in these patients[39,62]. There is involvement of multiple organ systems; lymph nodes, skin, bone, and soft tissue seem to be most commonly impacted[39,62]. Infections can also occur in the bone marrow or blood, lung, bladder, liver, and biliary tree[15,19,24,39]. It is probable that there will be variations in the clinical presentations, sites of infection, and etiological agents among different ethnic groups. The most often isolated NTM species from Thai, Chinese, and Filipino patients were rapidly growing mycobacteria (RGM), such as *M. abscessus*, while *M. avium* complex (MAC) was more common in Japanese and non-Asian patients. Individuals with RGM were more likely to have lymph nodes implicated than individuals with MAC, who were more likely to have lung and bone infections.

Disseminated NTM in individuals with anti-IFN-γ autoantibodies has been shown in numerous investigations to mimic cancer, malignancy, and the synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome[22,69,71]. As a result, differential diagnosis needs to be used carefully. Even though the majority of patients clinically present with disseminated infections, it is crucial to assess antibody detection given the importance of anti-IFN-γ Aabs-associated pathogenesis. Nowadays, there is a wide range of methods employed to assess anti-IFN-γ Aabs in suspected cases with specific infections, from quick tests to time consuming, lengthy bioassays.

The many diverse techniques, including biological activity assays and qualitative or quantitative IFNγ-specific binding, are compiled based on earlier studies. The enzyme-linked immunosorbent assay (ELISA), either in an indirect[42,12,72–79] or an inhibitory[42,63,67,70,72,76,80–84]. Assay format, is the most widely used test to identify anti-IFN-γ Aabs. The results of the ELISA-based procedure can be expressed quantitatively as optical density (OD)[77] titer[81], or qualitatively as positive or negative. They can also be calculated using arbitrary units (UN) or ELISA units (EU)[75,77]. The inexpensive, user-friendly Dot ELISA strip was created as a point-of-care screening tool in remote settings. It can be read immediately on the strip[65,85].

A particle-based test that purports to be a quick, simple, and reasonably priced method has also been utilized to find many anti-cytokine autoantibodies in human plasma at once[15,64,73]. The commercialized IFN-γ release assay QuantiFERON-TB Gold In-tube (QFT-GIT), which is frequently utilized in hospitals to identify latent tuberculosis, has been adapted to screen for neutralizing anti-IFN-γ antibodies[22,84]. The high throughput quantitative Luciferase Immunoprecipitation System (LIPS) is a helpful tool for simultaneously detecting many anti-cytokine autoantibodies. Additionally, IFN-α immunoblots have been employed to confirm the precise type of binding activity[1,65,78,82].

4.3. HLA-DRB1 and HLA-DQB1 are associated with adult-onset immunodeficiency with acquired anti-interferon-gamma autoantibodies

A newly identified clinical syndrome involving disseminated non-tuberculous mycobacterial (NTM) diseases in adult patients, previously healthy, has been recognized in association with an acquired autoantibody to interferon-gamma (IFN-γ). This syndrome is becoming a significant cause of morbidity and mortality, particularly among individuals of Asian descent[10]. While the trigger for the production of this autoantibody remains unknown, genetic factors are strongly suspected to be involved. Numerous studies have shown that Human Leukocyte Antigen (HLA) genes are linked or play a crucial role in the pathogenesis of various autoimmune diseases, adverse drug reactions, and increased susceptibility to certain infections[85–89].

Recent studies have highlighted a high prevalence of autoantibody to IFN-γ in previously healthy, non-HIV-infected adult Thai patients with disseminated NTM disease[10]. In a genetic study involving a subgroup of 10 patients followed up at a hospital, all anonymous healthy blood donors from that study, and six patients with active pulmonary tuberculosis as controls, all cases in the study exhibited detectable autoantibody to IFN-γ.

The role of HLA in various immune disorders has been well-described. Specific HLA genotypes are associated with autoimmune diseases such as rheumatoid arthritis, ankylosing spondylitis, and type 1 diabetes[88–91]. Additionally, Stevens-Johnson syndrome and toxic epidermal necrolysis related to carbamazepine and allopurinol are also associated with specific HLA genotypes in the Asian population[85,86]. The inclusion of genetic factors in the investigation helps shed light on the complex interplay between host genetics and the development of autoimmune and infectious diseases. In addition to the previously observed strong association with DRB116:02 and DQB105:02 in a Taiwanese cohort, the Thai cohort in this study revealed an association with HLA-DRB115:01 and DQB105:01. Notably, HLA-DRB116:01 and DRB116:09 were exclusively found in the case group. This data suggests that the HLA-DRB115 and DRB116 subgroup, rather than each specific allele, is associated with the identified syndrome. It's important to note that HLA-DRB116:02 and DQB105:02 are more prevalent in Asian populations compared to Caucasian populations. However, HLADRB115:01 and DQB105:01 are found to be similarly common among Caucasian and African American populations as in the Thai population[92].

In conclusion, this study represents the largest cohort of patients demonstrating a robust association between HLA-DRB1 and DQB1 alleles, especially HLA-DRB115:01, DRB116:02, DQB105:01, and DQB105:02, and disseminated opportunistic infection with acquired anti-IFN-γ autoantibody. Despite the clear association, the mechanism explaining this link remains unknown. Further investigation is warranted to

provide a better understanding of the pathogenesis underlying this syndrome[90].

Related to the above condition, it is important to involve multidisciplinary care involving infectious disease specialists, immunologists, geneticists, and other healthcare professionals in the comprehensive management of affected individuals, as well as the need for coordinated care and individualized treatment plans.

5. Related disease

Anti-IFN-γ autoantibodies play a key role in common Talaromyces marneffei infections. Talaromyces marneffei is a significant intracellular fungal pathogen capable of causing serious systemic infections. This thermally dimorphic fungus transforms from septate hyphae at 25 ℃ to a pathogenic yeast morphology at 37 ℃ during infection. It is endemic to specific regions, including southern China, Taiwan, Thailand, Laos, Vietnam, northeastern India, and Hong Kong, with almost exclusive confinement to the southeast[1]. The geographic and ethnic distribution of risk-related HLA haplotypes explains the regional limitation of diseases associated with anti-IFN-γ autoantibodies. Due to the high frequency of the risk haplotype DRB1 in southern China, especially in Guangxi, it was hypothesized that this region would also have a high prevalence of anti-IFN-γ autoantibodies. To test this hypothesis, the presence of anti-IFN-γ autoantibodies and HLA class II haplotypes was analyzed in HIV-negative patients with *T. marneffei* infection from southern China[93].

The production of neutralizing autoantibodies against IFN-γ is an emerging adult immunodeficiency observed in certain regions of the world, including Hong Kong, Thailand, and Taiwan. Occasional cases have also been reported in Japan, the Philippines, Vietnam, Laos, and other Southeast Asian countries. Patients with neutralizing anti-IFN-γ autoantibodies often experience disseminated infections, and other opportunistic infections, such as *T. marneffei* infection, have been observed in some patients with anti-IFN-γ autoantibodies[94–98]. The biological activity of these anti-IFN-γ autoantibodies was assessed by evaluating their ability to neutralize IFN-γ-induced HLA-DR expression and STAT-1 phosphorylation in THP-1 cells. Plasma from all anti-IFN-γ autoantibody-positive patients demonstrated a reduction in IFN-γ-induced HLA-DR expression and STAT-1 phosphorylation. In contrast, plasma from healthy donors or antibody-negative patients showed no inhibitory effect. IFN-γ has been shown to enhance the clearance of *T. marneffei* in myeloid cells, and plasma from patients positive for anti-IFN-γ autoantibodies was found to attenuate IFN-γ-mediated *T. marneffei* in THP-1 cells[99–103].

5.1. Clinical manifestations, course, and outcome of patients with neutralizing anti-interferon-g autoantibodies and disseminated nontuberculous mycobacterial infections

Immunodeficiency caused by neutralizing anti-interferon-gamma autoantibodies (nAIGAs) with severe or disseminated mycobacterial infection is a recently emerging medical issue, particularly prevalent in Southeast Asia. Over the past decade, approximately 190 individuals, including those described in your study, with nAIGAs have been reported in the literature[20,23]. The majority of these cases are of Asian descent and are primarily from Thailand and Taiwan. This aligns with the prevalence rate of 81%–96% reported by Browne et al.[11].

Non-tuberculous mycobacteria (NTM) are environmental microorganisms, and their distribution is dependent on geographic location, especially in Asian countries. For instance, in Hong Kong, South Korea, and Taiwan, slow-growing non-tuberculous mycobacteria (SGNTMs) are the most frequently reported clinical isolates[104,105]. The emergence of immunodeficiency associated with nAIGAs poses a significant health concern in the region, emphasizing the importance of understanding and addressing this phenomenon.

5.2. Clinical implications of interferon-γ genetic and epigenetic variants

IFN-γ is a significant activator of macrophages, promoting the production of tumor necrosis factor-alpha

(TNF-α). This collaboration between IFN-γ and TNF-α enhances macrophage phagocytosis and microbicidal activity, including the generation of reactive nitrogen and oxygen species such as superoxide radicals, nitric oxide, and hydrogen peroxide. Furthermore, IFN-γ contributes to lymphocyte recruitment, resulting in prolonged activation within tissues. It induces components of the complement cascade and the acute phase response, plays a role in IgG class switching, and exhibits direct anti-viral effects.

In the context of immune response, IFN-γ is crucial in controlling the differentiation of naive CD4 T-cells into Th1 effector T-cells, which are critical mediators of cellular immunity against viral and intracellular bacterial infections. The IFN-γ gene is subject to both genetic and epigenetic variations, some of which have been associated with gene expression and various diseases[105–108].

6. Recent treatment and potential application

6.1. Daratumumab (Anti-CD38) for treatment of disseminated nontuberculous mycobacteria in a patient with Anti–Interferon-γ autoantibodies

The described case presents a novel use of daratumumab in a patient with autoantibodies to interferon-γ (IFN-γ) who had a progressive mycobacterial infection despite multiple cycles of rituximab. Patients with such autoantibodies often face severe and progressive infections with *mycobacteria* and other intracellular pathogens, even with aggressive antimicrobial treatment.

Previous studies have shown that rituximab can improve symptoms, disease burden, and mycobacteremia, along with decreasing anti-IFN-γ autoantibody titers in patients with similar conditions. However, persistently high titers despite rituximab treatment can lead to progressive and potentially fatal diseases. In this case, daratumumab, an anti-CD38 monoclonal antibody approved for treating multiple myeloma, was used, resulting in clinical and radiographic improvement.

A study evaluating daratumumab's effect on autoantibody titers reported a significant reduction in titers in patients undergoing treatment for multiple myeloma. The successful use of daratumumab has also been reported in life-threatening autoimmune hemolytic anemia and pure red cell aplasia after an ABO-incompatible hematopoietic stem cell transplant

This case suggests that daratumumab could be another potentially effective therapeutic agent for patients with anti-IFN-γ autoantibodies who are refractory to rituximab. Notably, while steroids were administered surrounding daratumumab infusions, they have not been found to be effective in managing autoantibodies to IFN-γ and may worsen *nontuberculous mycobacteria* (NTM) infections. This report represents the first successful use of daratumumab in the setting of IFN-γ autoantibodies refractory to optimal antimycobacterial medication and rituximab[109].

6.2. Rituximab as successful adjunct treatment in a patient with disseminated nontuberculous mycobacterial infection due to acquired anti–interferon-γ autoantibody

Individuals with immunodeficiency due to defects in the interleukin 12 (IL-12) and interferon-gamma (IFN-γ) pathways may develop disseminated infections with nontuberculous mycobacteria (NTM). These immunodeficiency syndromes can be either heritable or caused by acquired autoantibodies to IFN-γ. Disseminated NTM infections in individuals with anti-IFN-γ autoantibodies are often challenging to treat and may not respond well to traditional antibiotics. Therapies targeting the autoantibody itself could be a valuable addition to conventional antibiotic treatments

The described case involves an elderly man with persistent disseminated *Mycobacterium abscessus* infection due to the presence of autoantibodies to IFN-γ. The patient was successfully treated with rituximab. Previous attempts to address anti-IFN-γ autoantibodies with IFN-γ administration, immune globulin, and plasmapheresis have been reported to be unsuccessful. Rituximab has shown promise in reducing autoantibody

titers, improving IFN-γ signaling, and achieving clinical remission in patients with anti-IFN-γ autoantibody syndrome.

The treatment of disseminated *M. abscessus* infections typically involves a rigorous combination of antimycobacterial therapy, sustained until immune restoration is achieved. The favorable response of the patient to rituximab adds to the growing body of evidence suggesting that rituximab may be an effective treatment for autoantibody-related immunodeficiency syndromes[110].

6.3. Severe paradoxical reaction during treatment of disseminated tuberculosis in a patient with neutralizing Anti-IFNγ autoantibodies

Interferon-gamma (IFN-γ) neutralizing autoantibodies have been linked to disseminated nontuberculous mycobacterial (NTM) infections. The case involves a previously healthy Thai woman who developed disseminated tuberculosis along with high-titer IFN-γ-neutralizing autoantibodies. Notably, the patient experienced a severe inflammatory reaction during anti-tuberculosis treatment.

IFN-γ plays a crucial role in host control of tuberculosis, contributing to macrophage activation and the control of mycobacteria and intracellular fungi. Autoantibodies to IFN-γ have been predominantly identified in individuals of Southeast Asian origin who suffer from disseminated NTM infections or other intracellular pathogens. This emphasizes the critical role of the IL-12/IFN-γ axis in controlling these infections.

Rituximab, a monoclonal antibody, has shown promise in reducing anti-IFNγ titers in refractory patients, leading to the clearance of mycobacterial infections. The report highlights the complex interactions between the immune system, infections, and the potential impact of autoantibodies on the course of diseases like tuberculosis[111].

6.4. Efficacy of acitretin in the treatment of reactive neutrophilic dermatoses in adult-onset immunodeficiency due to interferon-gamma autoantibody

This study underscores the significant efficacy of acitretin in treating neutrophilic dermatoses associated with Adult-Onset Immunodeficiency (AOID). The rash showed substantial improvement within two weeks with a daily dosage of 10–25 mg of acitretin in the majority of patients. The mean time to the initial response was 5.6 days, comparable to the reported duration for treating pustular psoriasis.

In terms of safety, the incidence of acitretin-induced hepatotoxicity in this cohort was low, affecting only one patient (3.7%), and the condition completely reversed upon discontinuation of acitretin. This is notably lower than the prevalence reported in the range of 21.3%–30.5%. Other adverse reactions like lipid abnormalities, cheilitis, and dry skin were not observed in this cohort. The potential teratogenic effect of acitretin, a significant concern in prescription, is deemed less worrisome in this context as the patients are generally not of childbearing age.

The study suggests acitretin as a first-line treatment for reactive neutrophilic dermatoses associated with AOID, citing its efficacy, tolerability, and lack of immunosuppressive effects, as demonstrated by a 10-year experience. However, the researchers emphasize the need for additional randomized controlled studies to validate these findings[112].

6.5. Intravenous cyclophosphamide therapy for Anti-IFN-Gamma autoantibody-associated *mycobacterium abscessus* infection

Anti-interferon-gamma (IFN-γ) autoantibodies have been recognized as a cause of adult-onset immunodeficiency (AOID) worldwide, rendering patients susceptible to various intracellular pathogens, particularly nontuberculous mycobacteria. The refractory clinical course observed in most of these patients poses a significant challenge. This report discusses the utilization of immunotherapy with pulse intravenous cyclophosphamide (IVCY) in individuals with progressive and refractory *Mycobacterium abscessus* infection.

The study suggests that IVCY therapy may serve as an alternative treatment for AOID patients infected with *M. abscessus* who do not respond to conventional antimycobacterial therapy.

The patients in this study exhibited extensive disease due to *M. abscessus* infection, with a median duration of infection lasting 17 months. Lymphadenitis was a common manifestation, along with infection in other sites, and most patients had coinfection with other opportunistic pathogens. Given the refractory nature of the infection to antimycobacterial treatment, adjunctive immunotherapy was explored. While rituximab has previously been used in AOID patients associated with mycobacterial infection, this report highlights the potential efficacy of pulse intravenous cyclophosphamide in such cases[84].

6.6. Benznidazole therapy modulates interferon-c and M2 muscarinic receptor autoantibody responses in Trypanosoma cruzi-infected children

The study investigated the production of anti-M2 muscarinic receptor autoantibodies (Anti-M2R Aabs) and the interferon-gamma (IFN-γ) profile in children at the early stage of Chagas disease. Additionally, the impact of trypanocidal chemotherapy with benznidazole (BZ) on these response patterns was examined. The results indicated that anti-M2R AAbs and IFN-γ levels are elevated early during Chagas disease in children and that these immune responses are downmodulated by BZ therapy. The findings suggest that early treatment with benznidazole not only helps eliminate the parasite but also reduces potentially pathogenic immune responses in Chagas disease[113].

7. Conclusion

Autoimmune diseases are increasingly being discussed nowadays. One of them is Adult-Onset Immunodeficiency Syndrome, which is an autoimmune disease due to a defect or damage to the function of IFN-γ, due to the production of antibodies from IFN-γ which results in a decrease in immune function in the body. Until now the cause of the appearance of these antibodies is not yet known. It is suspected that several genetic mutations were the trigger for this incident. Control efforts with research on the immune pathogenesis of this disease are currently in the process of being explored more deeply. And until now, various treatments have begun to be found to overcome this impaired function of IFN-γ. It is hoped that in the future research on this syndrome will continue so that the main cause can be found and the morbidity rate can be reduced by exploring more about the advancements of its immunopathology in the field of IFN-γ biology, hopefully, the novel therapeutic targets, and unanswered questions that warrant further investigation could get the answer.

Furthermore, research related to expanding on potential therapeutic strategies or interventions aimed at mitigating the effects of these autoantibodies could provide valuable insights for clinicians and researchers. Last but not least, the additional epidemiological insights, prevalence, and distribution of IFN-γ autoantibody-associated immunodeficiency syndromes also need to be investigated more.

Funding

The study received financial support from the National Science and Technology Council, Taiwan (NSTC 112-2113-M-038-005).

Conflict of interest

The authors declare no conflict of interest.

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