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Andes pediatr. 2025;96(2):181-190
DOI: 10.32641/andespediatr.v96i2.5237

ORIGINAL ARTICLE

Incidence of infections in pediatric patients using biological therapy

Incidencia de infecciones en pacientes pediátricos usuarios de terapia biológica

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Received: April 22, 2024; Approved: October 28, 2024

What do we know about the subject matter of this study?

Immune-mediated diseases have benefited greatly from the emergence of biologic therapies by changing their clinical course. The theoretical risk of infections associated with their use has been poorly studied in children, especially in developing countries.

What does this study contribute to what is already known?

This study shows a low rate of infectious complications and that biologic therapies present a good safety profile in terms of infectious complications, with no reports of important repercussions during respiratory, gastrointestinal, genitourinary, musculoskeletal, skin and soft tissue infections, reactivation of tuberculosis, and hepatitis B, regardless of the underlying pathology. It provides information to both physicians and patients on the use of these increasingly used therapies.

Abstract

Biological therapies have improved the prognosis of patients with inflammatory diseases. In adults, an increased risk of presenting infections has been reported, however, there are few pediatric studies. **Objective**: to describe the incidence of infections in pediatric patients using biological therapies. **Patients and Method:** Retrospective cohort study of pediatric patients with rheumatic diseases and inflammatory bowel diseases, treated with biological therapies, at the UC-Christus Health Network between 2007-2019. The number, type, and characteristics of mild and serious infections (hospitalization requirement, use of intravenous antimicrobials, association with mortality) were recorded. Descriptive statistics were used. **Results:** We included 128 patients diagnosed with juvenile idiopathic arthritis (89.8%), primary vasculitis (3.9%), and inflammatory bowel disease (3.1%). Adalimumab was used in 43.9%, Etanercept in 22.5%, and Tocilizumab in 16.8% of patients. 52.6% of patients reported an infection. The most common mild infections were upper respiratory tract infections (61.5%) and lower respiratory tract infections (10.6%). The most frequent severe infections were gastrointestinal infections (2.9%) and lower respiratory tract infections (2.3%). The incidence rate

Keywords:
Biological Therapy;
Infections;
Immunosuppression;
Safety Profile;
Pediatrics

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Edited by:
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How to cite this article: Andes pediatr. 2025;96(2):181-190. DOI: 10.32641/andespediatr.v96i2.5237

of mild infections was 119.7 (CI 106-128) per 100 person-years and the incidence rate of severe infections was 10.3 (CI 73.7-142.1) per 100 person-years. No cases of reactivation of tuberculosis or hepatitis B virus were observed. There were no hospitalizations in intensive care units, deaths, or need to suspend biological therapy due to infections. **Conclusions:** This study shows that biological therapies have a good safety profile, without reports of significant repercussions during infections, regardless of the underlying pathology.

Introduction

Biologic therapies are therapies based on monoclonal antibodies or fusion proteins, genetically designed to modulate the function of the immune system, acting specifically on key proteins involved in the immune response associated with inflammatory diseases[1,2,3]. Such chronic diseases involve morbidity and potentially disability, so their appropriate management is crucial. Biologic therapies are currently a therapeutic alternative for patients with poor response to conventional therapies[4], improving their physical and functional prognosis[1,3-6]. Despite the benefits associated with their use, adverse effects are reported, such as increased risk of infections, allergic reactions of varying severity (mild to anaphylaxis), and neoplasms, among others. Infections are one of the most frequently described unfavorable events[7,8]. Considering that biologic therapies modulate the function of the immune system[9] and that the pediatric population has a high exposure to infectious agents, children represent a group potentially more susceptible to present infections secondary to these therapies.

An increased risk of bacterial infections, typical and atypical, tuberculosis (TB) reactivation or *de novo*, varicella zoster virus (VZV) infections, hepatitis B virus (HBV) reactivation, and fungal infections are described in adult patients using biologic therapies[10-14]. A Cochrane systematic review, which evaluated the safety of 9 biologic drugs in people older than 16 years, showed an increased risk of serious infections (OR 1.3; 95% CI 1.1-1.8; p = 0.15) and increased risk of TB reactivation (OR 4.6; 95% CI 1.2-18.6; p = 0.028)[10]. Another systematic review also showed an increased risk of severe infections in children with juvenile idiopathic arthritis (JIA) using biologics (OR 1.2; 95% CI 0.8-1.7; p = 0.543)[11]. Besides, Diener et al described an incidence rate of severe infections of 0.05 events/person-years in patients with JIA[12].

The type of infections presented by users of biologic therapies varies according to the drug used. In anti-TNF-α users (adalimumab, infliximab, etanercept, and golimumab), a higher risk of presenting pneumonia, abscesses, *listeria* spp infections, VZV infections, and granulomatous diseases (TB, histoplasmosis, and coccidioidomycosis) has been described. In addition, an increased risk of presenting infections by herpes simplex virus, VZV, upper respiratory tract infections, and visceral leishmaniasis has been associated with users of IL-2 inhibitors (Anakinra or Canakinumab). IL-6 inhibitors, such as tocilizumab, have been associated with an increased risk of respiratory infections (upper respiratory tract infections, pneumonia, bronchitis) and skin and soft tissue infections (cellulitis or chickenpox). Finally, rituximab (anti-CD20) is associated with an increased risk of presenting viral infections (varicella, cytomegalovirus, adenovirus, HBV reactivation), respiratory infections (pneumonia, empyema), mastoiditis, and gastrointestinal infections (*Salmonella* spp, candidiasis)[15,16].

Despite the studies, the evidence in the pediatric population continues to be insufficient and is limited to the report of serious infections, so that the incidence rate of non-serious infections could be underreported[10-12]. Besides, there is significant regional variability in the occurrence of infections, considering the epidemiology and sociodemographic variables of the populations[17], which makes the study of the safety of the use of biologic therapies in children in developing countries more relevant, as environmental conditions could represent an additional risk factor. Our objective is to characterize the type and incidence of infections in pediatric patients using biologic therapies.

Patients And Method

Design

Descriptive retrospective cohort study, non-concurrent, of pediatric patients with autoimmune or inflammatory diseases, attended in a referral center (UC Christus Health Network) in Santiago, Chile, from January 2007 to December 2019. The follow-up ended in December 2019, given the possibility of subsequent underreporting of the infections presented, considering the decrease in medical check-up visits in the context of confinement due to the SARS-CoV-2 pandemic.

The Pediatric Rheumatology and Gastroenterology units of the institution have records of patients with rheumatologic diseases and inflammatory bowel

disease who maintain follow-up in this health center. The records were reviewed, and the patients were selected from the cohort studied after applying the inclusion and exclusion criteria. Inclusion criteria were to be under 18 years of age and to be a user of biologic therapy for the treatment of the pathologies previously described. The exclusion criteria were onco-hematologic pathologies, human immunodeficiency virus (HIV), and hematopoietic precursor or solid organ transplants because they could present a higher risk of infection associated with their underlying pathologies and/or treatments.

Non-serious and serious infections were recorded, defining serious infections as all infections that required hospitalization, use of intravenous antimicrobials (antibiotics, antivirals, antifungals), or were associated with mortality; the rest of the infections were considered non-serious.

Data collection

The outpatient, inpatient, and emergency department records of the cohort were reviewed. Follow-up began at the time of initiation of each biologic therapy and concluded at the end of its use or at the end of the follow-up period (December 2019). The characteristics of each individual were recorded (age at diagnosis, age at initiation of biologic therapy, gender, underlying pathology, comorbidities, biologic therapy used, date of start and end of administration of each biologic therapy, concomitant use of corticosteroids or other immunomodulators), the number of non-serious infections and type [upper respiratory tract (URT), lower respiratory tract (LRT), gastrointestinal, genitourinary, bone, skin, and systemic), the number of serious infections and type, the presence of TB, HBV, VZV (latent, reactivation, primary infection), the number of outpatient visits, emergency consultations and hospitalizations, days of hospitalization, days of intravenous antimicrobial use and total days in serious infections, days of hospitalization in the critical patient unit (CPU), and deaths.

Follow-up of infections

Before the start of each biologic therapy, an active search for latent TB, HBV, and VZV infection was performed, according to local protocols, in order to administer the necessary prophylaxis to avoid reactivation of latent infections or primary infections after the start of biologic therapy. History of non-serious infections was obtained mainly from the clinical records of outpatient visits and emergency department consultations. The diagnoses of non-serious infections were made by clinical criteria and there was no routine microbiological etiological study. The medical check-ups were performed at least monthly during the first year of treatment and were subsequently spaced according to the level or degree of control of their underlying pathologies. Serious infections were recorded from outpatient clinical records, emergency department consultations, and hospitalizations. In all cases of serious infections, a microbiological study was performed according to the patient's clinical condition.

Ethical aspects

The research was approved by the Scientific Ethical Committee of Health Sciences of the *Pontificia Universidad Católica de Chile* (ID 210116001, 11-03-2021).

Statistical analysis

The data were analyzed using Microsoft Excel and OpenEpi software version 3.01. Descriptive statistics were used to evaluate the characteristics of the cohort. Calculations of the proportions of patients according to gender, age at diagnosis, underlying pathology, comorbidities, and the number of biologic therapies used per patient, and were performed based on the number of individuals in the cohort. In individuals who used > 1 biologic therapy (not simultaneously), calculations of the parameters; time of biologic therapy use, type of biologic therapy used, concomitant use of corticosteroids or immunomodulators, number of outpatient visits, emergency department consultations, number of hospitalizations, days of intravenous antibiotic use, days of stay in CPU due to infections, and incidence rates; were performed based on the "period of biologic therapy use", defined as the period of use of each biologic drug separately. Rates were calculated by dividing the number of infections by the time of the episode of biologic therapy use, multiplied by 100 person-years.

Results

402 clinical records of patients with rheumatologic diseases and inflammatory bowel disease were reviewed, of which 132 met the inclusion criteria. Finally, data from 128 patients were analyzed after excluding 4 patients because they had incomplete records (Figure 1).

The 128 patients using biologic therapies accounted for 173 periods of biologic therapy, with a median duration of each period of 1.3 years [interquartile range (IQR) 2.3]. The sum of follow-up years during the total of the 173 periods of biologic therapies was 347.1 person-years. 97 patients in the cohort were female (75.8%), with a median age at diagnosis of their underlying pathology of 9 years (IQR 8). The main underlying pathology of the patients was JIA in 115 patients (89.9%) followed by primary vasculitis with 5 cases (4%) (Table 1).

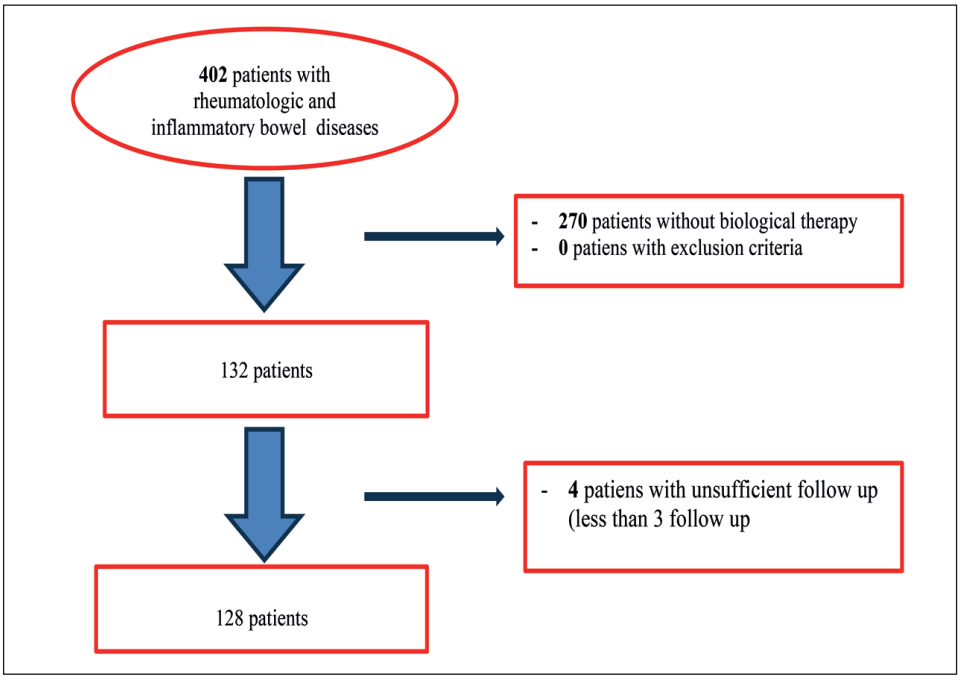

Figure 1. Study design.

The most frequently used biologic therapies during the biologic therapy periods (173) were adalimumab 76 (43.9%), etanercept 39 (22.5%), tocilizumab 29 (16.9%), and infliximab 10 (5.8%). During the follow-up period, 75% (96/128) of the patients used only 1 biologic therapy, while the rest > 1. Systemic corticosteroids were used concomitantly in 124 periods (71.7%), and immunomodulators in 119 (68.8%), with methotrexate being the most used in 112 periods (94.1%) (Table 1).

In relation to patient follow-up, patients had a median of 7 (IQR 9) outpatient visits, 0 (IQR 0, interval 0-15) emergency department consultations, and 0 (IQR 0, interval 0-39) hospitalizations (Table 1). No cases of poor adherence to biologic therapy were reported in our series.

Infections

Of the 173 periods of biologic therapy, only non-serious infections were recorded in 69 periods (39.9%), in 5 periods (2.9%) there were only serious infections, and in 17 periods (9.8%) both non-serious and serious infections occurred. The total number of infections presented during the 173 periods was 442, with 406 (91.9%) non-serious infections and 36 (8.1%) serious infections. Of note, there were periods of biologic therapies in which > 1 infection occurred. The median number of non-serious infections per biologic therapy period was 0 (IQR 3.2) and that of serious infections was 0 (IQR 0, range 0-6). 55.4% of infections occurred during the first 6 months of use of each biologic therapy (Table 2).

Of the 36 serious infections, 38.8% (14/36) were bacterial infections, 50% (18/36) were viral, and in 11.2% (4/36) the microorganism was not identified. There were no cases of TB or HBV reactivation (Table 3).Antimicrobials were used in 15.4% (68/442) of total infections (non-serious and serious), 11.6% (48/406) of non-serious infections, and 55.5% (20/36) of serious infections. The 16 cases of serious infections in which antimicrobials were not used corresponded to LRT or gastrointestinal viral infections that were hospitalized due to the need for oxygen therapy or intravenous hydration. The median number of days of intravenous antimicrobial use in sssserious infections was 5 days (IQR 3) and the median total antimicrobial use (intravenous and oral) was 10 days (IQR 10). There were no CPU admissions, deaths, or need to postpone or discontinue biologic therapy due to infections.

When evaluating the location of the infections, the most frequent non-serious infections were those of the URT (272/442, 61.5%) followed by LRT (47/442, 10.6%), while serious infections occurred mostly at the gastrointestinal level (13/442, 2.9%) and LRT (10/442, 2.3%). The etiology of serious gastrointestinal infections was mostly viral (8/442, 1.8%), with norovirus detected in 4/442 of cases (0.9%), followed by rotavirus in 3/442 of cases (0.7%). The second cause of serious gastrointestinal infections was bacterial, with *Clostridioides difficile* toxin isolated in 3/442 infections (0.7%). The main etiology of serious LRT infections was viral (6/442, 1.4%), with respiratory syncytial virus detected in 3/442 cases (0.7%), influenza in 2/442 cases (0.5%),

and metapneumovirus in 1/442 cases (0.2%). Serious bacterial LRT infections were reported in 3/442 (0.7%) cases. In 1 of the 10 serious LRT infections (1/442, 0.2%), the pathogen could not be isolated. During follow-up, 4 serious systemic infections were recorded, all of which corresponded to chickenpox, representing 0.9% of the total infections. It should be noted that all of these occurred in unvaccinated patients (Table 3).

Infection incidence rate

The overall incidence rate of infections (non-serious and serious) was 127.3 per 100 person-years (95%CI 115.9-139.7). When the incidence rates of infections were broken down according to severity, 119.7 per 100 person-years (95%CI 106-128.8) of non-serious infections and 10.3 per 100 person-years of serious infections (95%CI 73.7-142.1) were observed (Table 4).

The highest incidence rates of total infections (non-serious and serious) were presented by abatacept therapy with 266.7 per 100 person-years (95%CI 123.8-506.4), followed by canakinumab with 262.5 per 100 person-years (95%CI 166.8-394.4), and rituximab with 254.5 per 100 person-years (95%CI 172.5-363.0). The biologic therapies showing the highest incidence rate of serious infections were infliximab with 25.9 per 100 person-years (95%CI 11.3-51.2), tocilizumab with 19.3 per 100 person-years (95%CI 1.0-33.5), and ritux-

Table 1. Patient characteristics and therapies

Variable		Variable	
Total number of patients, n	128	*Inhibitor IL-6*	
Total number of biologic therapy periods, n	173	Tocilizumab, n (%)	29/173 (16,9%)
Person-years during follow-up, n	347.1	*Anti CD20*	
Duration of each biologic therapy period (years), median (RIC)	1.3 (2.3)	Rituximab, n (%)	7/173 (4,0%)
Age at diagnosis of baseline pathology (years), median (RIC)	9 (8)	*Inhibitor IL-2*	
Age at initiation of biologic therapy (years), median (RIC)	10 (7.5)	Canakinumab, n (%)	4/173 (2,3%)
Gender		*Inhibitor T cells co-stimulation (CTLA 4-Ig)*	
Female, n (%)	97/128 (75.8%)	Abatacept, n (%)	5/173 (2,9%)
Male, n (%)	31/128 (24.2%)	Number of biological therapies	
Baseline pathology		1, n (%)	96/128 (75,0%)
Juvenile idiopathic arthritis, n (%)	115/128 (89.9%)	2, n (%)	23/128 (18,0%)
Primary vasculitis, n (%)	5/128 (4.0%)	3, n (%)	6/128 (4,7%)
Inflammatory bowel disease, n (%)	4/128 (3.3%)	4, n (%)	3/128 (2,3%)
Systemic lupus erythematosus, n (%)	1/128 (0.7%)	Systemic corticosteroids	
Morphea, n (%)	1/128 (0.7%)	Yes, n (%)	124/173 (71,7%)
Anterior uveitis, n (%)	1/128 (0.7%)	No, n (%)	49/173 (28,3%)
Mixed connective tissue disease, n (%)	1/128 (0.7%)	Immunomodulators	
Comorbidities		No, n (%)	54/173 (31,3%)
Anterior uveitis, n (%)	12/128 (57.1%)	Yes, n (%)	119/173 (68,8%)
Primary vasculitis, n (%)	4 /128 (19%)	Methotrexate, n (%)	112/173 (64,7%)
Juvenile idiopathic arthritis, n (%)	1/128 (4.8%)	Mycophenolate, n (%)	3/173 (1,7%)
Systemic lupus erythematosus, n (%)	1/128 (4.8%)	Leflunomide, n (%)	2/173 (1,2%)
Autoimmune hepatitis, n (%)	2/128 (9.5%)	Mesalazine, n (%)	1/173 (0,6%)
Hypothyroidism, n (%)	1/128 (4.8%)	Azathioprine, n (%)	1/173 (0,6%)
Biologic therapies		Medical evaluations for each period of biologic therapy	
Anti-TNF		Outpatient checkups, median (RIC)	7 (9)
Adalimumab, n (%)	76/173 (43.9%)	ED consultations, median (RIC), *interval	0 (0), *(0-15)
Etanercept, n (%)	39/173 (22.5%)	Hospitalizations, median (RIC), *interval	0 (0), *(0-39)
Infliximab, n (%)	10/173 (5.8%)	Number of biologic therapies	
Golimumab, n (%)	3/173 (1.7%)		

n: number of individuals, IQR: interquartile range, *interval, Anti-TNF: anti-tumor necrosis factor, IL-6: interleukin 6, IL-2: interleukin 2, ED: emergency department, Number of biologic therapies.

Table 2. Characteristics of infections according to periods of use of biologic therapies

Variable	
Biological therapy periods without infections	82/173 (47.4%)
Biological therapy periods with infections	
Non-serious infections, n (%)	69/173 (39.9%)
Serious infections n (%)	5/173 (2.9%)
Non-serious and serious infections, n (%)	17/173 (9.8%)
Number of infections during total biological therapy periods	
Total infections, n	442
Non-serious infections, n (%)	406/442 (91.9%)
Serious infections n (%)	36/442 (8.1%)
Median of infections according to severity during biological therapy periods	
Non-serious infections, median (RIC)	0 (3.2)
Serious infections, median (RIC)	0 (0); *(0-6)
Timing of occurrence of serious infections according to time of onset of each period of biologic therapy	
< 3 months	10/36 (27.7%)
3-6 months	10/36 (27.7%)
6-12 months	4/36 (11.1%)
> 12 months	12/36 (33.3%)
Type of microorganism in serious infections	
Bacterial	14/36 (38.8%)
Viral	18/36 (50%)
No identification	4/36 (11.2%)
Antimicrobial use	
Total infections	68/442 (15.4%)
Non-serious infections	48/406 (11.6%)
Serious infections	20/36 (55.5%)
Days of antimicrobial use	
Serious infections	
Endovenous, median (RIC)	5 (3)
Total (oral + intravenous), median (RIC)	10 (10)
Duration of hospitalization for serious infections (days), median (RIC)	5 (3)
Hospitalization in CPU (days)	0
Deaths	0
Suspension of biologic therapy due to infections	0

SD: standard deviation, IQR: interquartile range, *interval, CPU: Critical Patient Unit.

imab with 18.1 per 100 person-years (95%CI 3.0-60.0). Supplementary Table 1 (online version available) presents the incidence rates of non-serious and serious infections for each biologic therapy when used as a first or second line of treatment.

Discussion

This study reported an incidence rate of non-serious and serious infections of 119.7 and 10.3 per 100 person-years, respectively, without observing cases of reactivation of diseases such as TB and HBV, hospitalizations in the CPU, or the need to suspend therapy due to infections. International literature describes a higher risk of infections in adult users of biologic therapies, with little data in pediatric age groups[10-14]. In our study, we observed low infection incidence rates (total), similar to the incidence rates of 0.5-2 events/person-years reported by Diener et al (2019)[12]. Moreover, the type of infections presented in our cohort also resemble those reported in previous studies[11-14]. Nagy et al (2019) showed that the most frequent global infections are URT, LRT, skin/soft tissue, and genitourinary infections[11]. When analyzing the types of serious infections, a higher risk of presenting LRT, genitourinary, and gastrointestinal infections is reported. Opportunistic infections are described as infrequent events, with VZV being one of the most reported[11-14,19,20].

The risk of infections varies according to the type of biologic therapy used. It is described that adalimumab, etanercept, and infliximab have a significantly higher relative risk of presenting infections than tocilizumab and abatacept[12-14]. In this series, a higher incidence rate of infections was observed in users of abatacept, canakinumab, and rituximab; however, the results may not be representative, considering the small number of patients using these biologic therapies, with adalimumab being the most widely used drug in our cohort (43.9%).

In our study, non-serious infections were more frequent than serious ones, however, they were reported in < 50% of the periods of biologic therapy, most of them being URT infections. As this is a retrospective study, the impact of these infections on the daily life of the users of biologic therapies in our cohort could not be evaluated (information not available in analyzed registries). However, they seem to have little impact, based on their low incidence rate, the infrequent consultation for the disease, and the reported duration of each infection. Another factor to consider is that the biologic therapies were administered in hospital units or transitional hospitalization units with accurate records of each biologic therapy infusion and with coverage by the Explicit Health Guarantees (GES) or under

Table 3. Type of infections according to periods of use of biological therapies

Variable	Number (%)
Type of non-serious infections	
URI	272/442 (61.5%)
LRI	47/442 (10.6%)
Skin	39/442 (8.8%)
Gastrointestinal	33/442 (7.5%)
Genitourinary	11/442 (2.5%)
Systemic	4/442 (0.9%)
Bone	0
Type of serious infections	
Gastrointestinal	13/442 (2.9%)
Virus	8/442 (1.8%)
Norovirus	4/442 (0.9%)
Rotavirus	3/442 (0.7%)
Adenovirus	1/442 (0.2%)
Bacterial	4/442 (0.9%)
Clostridiodes difficile	3/442 (0.7%)
Enteropathogenic *Escherichia coli*	1/442 (0.2%)
No pathogen identification	1/442 (0.2%)
URT (pneumonia)	10/442 (2.3%)
Viral	6/442 (1.4%)
Respiratory Syncytial Virus	3/442 (0.7%)
Influenza	2/442 (0.5%)
Mycoplasma pneumoniae	1/442 (0.2%)
No pathogen identification	3/442 (0.7%)
Genitourinary	1/442 (0.2%)
Bacterial	1/442 (0.2%)
Escherichia coli	1/442 (0.2%)
Klebsiella pneumoniae	1/442 (0.2%)
Enterococcus faecalis	6/442 (1.4%)
No pathogen identification	6/442 (1.4%)
Systemic infections	4/442 (0.9%)
Chickenpox (VZV)	1/442 (0.2%)
Skin	1/442 (0.2%)
No pathogen identification	0/442 (0%)
Bone	4/442 (0.9%)
Bacterial	4/442 (0.9%)
Staphylococcus aureus	2/442 (0.5 %)
URT	2/442 (0.5%)
TB reactivations	1/442 (0.2%)
TB (reactivation or de novo)	1/442 (0.2%)
HBV (reactivation or de novo)	1/442 (0.2%)
Type of non-serious infections	0
URT	0
LRT	0
Skin	0

TRS: tracto respiratorio superior, TRI: tracto respiratorio inferior, TBC: tuberculosis, VHB: virus hepatitis B, VVZ: virus varicela zóster.

Table 4. Incidence rates of infections per 100 person-years

Variable	Incidence rate
Total infections (n = 442)	127.3 (IC 115.9-139.7)
Non-serious infections (n = 406)	119.7 (IC 106.0-128.8)
Serious infections (n = 36)	10.3 (IC 73.7-142.1)

n: number of individuals, CI: confidence interval.

the Ricarte Soto Law, which ensures that the therapies were effectively administered and good adherence to the therapies in the cohort. In relation to our results, which coincide with those described in the referred reviews[11,12], the biologic therapies included in this work seem to be safe from the infectious perspective, with short hospital stays in serious infections, no admissions to CPU, deaths, or need to suspend or discontinue treatment due to their occurrence.

55.4% of serious infections occurred during the first 6 months of each biologic therapy period, which is similar to the results of other cohorts, which show mean times of occurrence of the first infection of 3-8 months after the initiation of each biologic therapy[21,22]. A possible explanation could correspond to the lower control of the underlying pathology during the first months of use of biologic therapy (with greater use of coadjuvant immunosuppressive therapies) and the lack of experience and/or initial adherence of patients in relation to self-care measures to prevent infections (hand washing, safe food, among others). However, we must consider that, during the first months of each period of biologic therapy, more frequent (monthly) medical check-ups are performed, which are spaced out as adequate control of the disease is achieved, so that some non-serious infections could be underreported at longer periods of use of biologic therapies.

Considering the risk of infections in biologic therapy users, among which TB, HBV, and VZV infections stand out, several scientific societies, including the Chilean Society of Infectious Diseases (2019), have published clinical guidelines on the screening and prophylaxis studies required for patients who will start biologic therapies[23-29]. The different clinical guidelines recommend systematically evaluating the history of VZV infection and vaccination status. If negative, it is suggested to perform a serological study with specific anti-VZV IgG to evaluate whether the patient should receive varicella vaccine. Considering that it is a live-attenuated vaccine, it should not be administered in patients with corticosteroid use (equivalent to prednisone at 1 mg/kg/day or 20 mg/day for 2 or more weeks) and it is necessary to wait at least 4 weeks post-vaccination for the initiation of biologic therapy,

which is often not possible to do, due to the need to achieve early control of the underlying disease. In such cases, it is suggested to vaccinate at-risk contacts, especially family members as a cocoon strategy[24-29].

In our cohort, 4/442 (0.9%) of the total number of infections corresponded to serious systemic infections, all of them being cases of chickenpox, which occurred in unvaccinated patients with intra-household contacts. In relation to TB, clinical guidelines suggest performing a latent infection screening study before initiating biologic therapy (especially anti-TNF-α), through clinical history, physical examination, tuberculin test or interferon-gamma release assay, and chest X-ray and prophylaxis should be administered in case of confirmation of latent TB[23,29]. In our cohort, 1 case of latent TB was observed, detected by the screening protocols currently performed on patients in our center, before the initiation of biologic therapies. The patient received prophylaxis according to local guidelines, without reactivation during follow-up. In this context, the protocols for screening and prophylaxis of infections in users of biologic therapies seem to be adequate and it is recommended to maintain them, with periodic updates.

The main limitations to consider in this study are that it included patients from only one center in the country, that most of the patients had the same underlying diagnosis (JIA), with a possible underrepresentation of other underlying pathologies, and that due to the retrospective design of the study, some non-serious infections could be underreported. However, its main strength is that it is the first Chilean study to show the characteristics and incidence rates of infections in pediatric patients using biologic therapies, in addition to including the report of non-serious infections during a prolonged follow-up (more than 12 years).

Conclusions

In our cohort, it was observed that the most frequent non-serious infections were URT viral infections, followed by LRT ones. In relation to serious infections, the main ones were gastrointestinal and LRT infections. In addition, the incidence rate of non-serious infections was 119.7 per 100 person-years and the incidence rate of serious infections was 10.3 per 100 person-years, with no cases of TB or HBV reactivation.

In conclusion, in this pediatric study, the use of biologic therapies demonstrated a good level of safety, since most of the infections presented in our cohort were non-serious infections and that, in serious infections, short hospital stays were observed, without admission to the CPU or deaths.

We believe that this study provides useful and reliable information for patients, their families, and treating physicians, at the time of initiating or during the use of a biologic therapy, in relation to the risk and profile of infections that they may present.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: This study was approved by the respective Research Ethics Committee, which, according to the study's characteristics, has accepted the non-use of Informed Consent.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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