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Biologic therapies committee. What does it provide?

Comisión de terapias biológicas. ¿Qué nos aporta?

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Abstract

Objective: To assess the general healthcare impact of a Biological Therapies Commitee (immune-mediated inflammatory diseases) through prescription habits, pre-biological studies and immunization.

Method: A quasi-experimental study was conducted on all naïve patients of legal age who started treatment with a biological agent for an immune-mediated inflammatory disease the year before and the year after the creation of the Biological Therapies Committee.

Results: A total of 31 patients treated in 2016 and 40 patients treated in 2018 were included. Prescriptions of tumor necrosis factor alpha inhibitor drugs decreased in 2018 (from 80.6% to 45.0%, $p < 0.05$), while prescriptions of interleukin 12/23 inhibitors increased (from 12.9% to 35.0%, $p < 0.05$). Tuberculosis screening was statistically different between the two periods: the number of interferon gamma release assays performed was higher in 2018 (from 9.7% to 80.0%, $p < 0.01$) and the proportion of patients who successfully underwent chemoprophylaxis was higher in 2018 (from 36.4% to 81.8%, $p < 0.05$). The proportion of tests requested for the study of viral pathologies and the number of vaccines administered were also higher in 2018.

Conclusions: The development of a specific Biological Therapies Committee allows healthcare improvements, contributing to a deeper understanding of the medications and to preventing the infection-related adverse events. It would therefore seem advisable to develop specialized committees akin to the Biological Therapies Committee in other domains.

KEYWORDS
Biological therapies; Autoimmune diseases; Committee; Biological products.

Resumen

Objetivo: Evaluar el impacto general a nivel asistencial de una comisión de terapias biológicas, en enfermedades inflamatorias inmunomediadas, mediante los hábitos de prescripción, los estudios prebiológicos y la inmunización.

Método: Se realizó un estudio cuasiexperimental sobre todos los pacientes *naïve* mayores de edad que iniciaron tratamiento con un medicamento biológico por enfermedad inflamatoria inmunomediada el año anterior y el año posterior a la creación de la comisión de terapias biológicas.

Resultados: Se incluyeron un total de 31 pacientes estudiados en 2016 y 40 pacientes estudiados en 2018. La prescripción de medicamentos inhibidores del factor de necrosis tumoral α se redujo en 2018 (80,6% *versus* 45,0%; $p < 0,05$), mientras que la prescripción de inhibidores de la interleucina 12/23 aumentó (12,9% *versus* 35,0%; $p < 0,05$). El cribaje tuberculoso fue estadísticamente diferente entre los periodos pre y postcomisión de terapias biológicas: la realización del *interferon gamma release assay* fue superior en 2018 (9,7% *versus* 80,0%, $p < 0,01$) y la proporción de pacientes que realizaron correctamente la quimioprofilaxis fue superior en 2018 (36,4% *versus* 81,8%, $p < 0,05$). La proporción de pruebas solicitadas para estudio de patologías víricas, así como la administración de vacunas, fueron superiores en 2018.

Conclusiones: El desarrollo de una comisión específica de terapias biológicas aporta mejoras asistenciales en enfermedades inflamatorias inmunomediadas, al contribuir a un mayor conocimiento relacionado con los medicamentos y con la prevención de los efectos adversos de carácter infeccioso, por lo que sería conveniente que se impulsara el desarrollo de comisiones especializadas como la comisión de terapias biológicas.

PALABRAS CLAVE
Terapias biológicas; Enfermedades autoinmunes; Comisión; Medicamentos biológicos.

Introduction

Immune-mediated inflammatory diseases (IMIDs) are chronic conditions with a common physiopathological basis, i.e. the loss of immune tolerance to autoantigens, which usually induces tissular, organic and even systematic damage. Because of their very nature, IMIDs tend to result in a heavy burden on the health system and significantly impact work productivity and quality of life[1].

Immunosuppressants constitute the gold standard in the treatment of IMIDs. Nonetheless, these medications are associated to multiple adverse events, which has prompted the search for a safer and more effective alternative. Such an alternative came along over 15 years ago with the development, and subsequent introduction, of the first biological drug (BD)[2]. The high effectiveness of such drugs revolutionized in the way patients were controlled and clinically managed. Since then, the use of these drugs has experienced a steady increase, having nowadays become part of the standard treatment not only of IMIDs but also of oncologic conditions[3].

It must be pointed out, however, that BDs are not innocuous medications. Indeed, they have been associated to an increased risk of infectious (both viral and bacterial) complications[4-6], including a higher incidence of tuberculosis (TB) particularly when BDs such as tumor necrosis factor (TNF)-alpha inhibitors like infliximab are used[7].

Use of BDs has become increasingly widespread in a growing number of medical specialties, where they are used with different approaches and modalities. Given that significant disparities still exist in terms of how to more efficiently use and manage BDs, multidisciplinary biological therapies committees (BTCs) have been established in different countries with a view to building consensus[8,9], apportioning responsibilities and ensuring uniformity and high quality in healthcare.

The overarching purpose of this study was to analyze the overall impact that the establishment of an IMID-targeted BTC has exerted on healthcare in our country. The specific aim was to compare the prescription habits observed before and after setting up the committee, and to identify any differences in the kind of tests requested as part of biological analyses and in the immunization administered to the patients studied before and after establishing the BTC.

Methods

This was a quasi-experimental before-and-after study with a non-equivalent control group, carried out in a 165-bed hospital with a catchment population of 220,000 people. Subjects were all BD-naive adult patients who had been put on treatment with a BD for an IMID the year before and the year after the BTC was established. The study went on for a total of three years and consisted of three periods: pre-committee period, period during which the committee was established, and post-committee period.

Patient selection was carried out using the two systems available at the hospital (Farmatools® 2.5 [Dominion] and xHIS 5.0), which provided information on the subjects' clinical and pharmacotherapeutic record. Annex I illustrates the data gathering sheet used. Patients who had previously received a BD (either experimentally or as part of their treatment) were excluded from the study. Patients who started their treatment at other hospitals were also excluded, as were patients whose clinical records contained ambiguous or contradictory data.

During the first period, the focus was on analyzing prescription patterns, conducting a pre-biological analysis and looking into the sociodemographic characteristics of patients who started treatment with at least one biological agent over the 12 months prior to the setting up of the BTC (January to December 2016).

The second period, which ran from January to December 2017, was the interval during which the committee was developed. The first phase was devoted to drawing up the work program and selecting the members of the committee and to preparing a schedule of meetings to review the existing literature and agree on a protocol for the use of BDs. Once the committee was under way and the treatment protocol established, a training program was implemented, which consisted of face-to-face sessions where the protocol was introduced and informational brochures were distributed to the hospital staff involved with administration of BDs.

The third period extended from January to December 2018 and was devoted to analyzing prescription patterns, conducting psychological tests and evaluating the sociodemographic characteristics of the subjects who started treatment with at least one BD.

The clinical and sociodemographic variables analyzed during the pre- and post-committee phases included age, gender, place of origin, indication for treatment with a BD, years of progression of the disease, and prescribing department. In addition, the pre-biological study carried out was evaluated in terms of the following variables: a) for TB screening we investigated which methods were used (purified protein derivative (PPD) test, interferon gamma release assay (IGRA) and chest radiographs), the results obtained and the therapeutic decisions adopted; b) for immunological screening we looked into whether a systematic review had been made of the subjects' vaccination schedule and whether the required serologic tests (hepatitis B virus [HBV], hepatitis C virus [HCV], hepatitis A virus [HAV], human immunodeficiency virus [HIV], rubella virus, smallpox virus, and measles virus) had been performed. The results obtained and the actions carried out were also analyzed. Lastly, vaccination against pneumococcus and influenza was evaluated.

For convenience, delivery of information to the patients as well as completion of the informed consent form were made to coincide with the patients' hospital appointments for dispensing and administration of the biological agent.

Quantitative variables are expressed as mean and standard deviation while qualitative ones are presented using frequency distribution. Pearson's chi-squared test was used to analyze the association between qualitative variables. In cases where the number of cells with expected values below 5 was higher than 20%, we used Fischer's exact test or the likelihood-ratio test for variables with more than two categories.

Comparisons of quantitative variables were made using either Student's t test or one-factor ANOVA for independent samples, as appropriate. Data were analyzed using the SPSS for Windows 2.0 software package. P values < 0.05 were considered statistically significant.

During the statistical analysis, an Excel file was created to process the collected data. To protect the confidentiality of the data, access to the file was restricted to users with a username and password. No copies were made of the data and none of it was disclosed via e-mail or other electronic means.

The study was reviewed by the hospital's Ethics Committee. We declared our commitment to uphold the principles of the Helsinki Declaration (Fortaleza, Brazil, 2013), the clinical practice guidelines and the regulations applicable to biomedical research (Act 14/2007 on biomedical research). We also vowed to guarantee data confidentiality in accordance with Act 3/2018 on the protection of personal data.

Results

The study comprised two groups. The first one was made up of 31 patients treated in 2016 while the second one comprised 40 patients treated in 2018. Only one patient (from the 2018 group) was excluded from the study because he had been referred from another hospital where he had been started on BD therapy. Table 1 shows the characteristics of the patients in both groups. No statistically significant differences were found between both groups in terms of age or gender. Nor were any differences observed in terms of the length of time during which the disease had evolved prior to the start of BD therapy, or in terms of the patients' place of origin.

Prescription patterns did undergo changes as a result of the establishment of the BTC. Indeed, once the committee was set up, a noticeable trend toward prescribing more innovative biological agents was observed. Prescription of anti-TNFα agents decreased significantly in 2018 (from 80.6% to 45.0%, $p < 0.05$), while prescription of interleukin inhibitors 12/23 experienced a considerable increase (from 12.9% to 35.0%, $p < 0.05$). No statistically significant differences were observed, however, in the proportion of prescriptions filled by different specialties (Table 2).

A comparison of the results of the pre-biologic studies conducted in 2016 and 2018 showed statistically significant differences regarding TB screening. Performance of IGRA was significantly more common in 2018 (from 9.7% to 80.0%, $p < 0.01$). The number of patients with a positive PPD result was statistically higher in 2016 (from 37.9% to 0,0%, $p < 0.001$). Conversely, the number of patients who performed their chemoprophylaxis in strict compliance with the protocol was statistically higher in 2018 (from 36.4% to 81.8%, $p < 0.05$). The amount of tests requested to rule out viral conditions (HBV, HCV, HAV, HIV, rubella, measles and smallpox) was higher in 2018 (Table 3).

When comparing the immunization administered to the two groups of patients, it was observed that the amount of patients treated in 2018 who had received the 13-valent pneumococcal conjugate vaccine (PnC13) before being examined was statistically higher than in the group treated in 2016 (from 0,0% to 12.4%, p = 0,050). An analysis of the vaccines given to patients as a result of the pre-biological study showed that the rate of administration of both PnC13 (from 25.8% to 92.5%, p < 0.001) and the 23-valent pneumococcal vaccine (Pn23) (from 64.5% to 97.5%, p < 0.001) was statistically higher in 2018 than in 2016. The indication and administration of vaccines to prevent viral conditions in both periods was not comparable as no serologic tests were requested in 2016 to find out about the patients' immunologic status (Table 4).

Table 1. Characteristics of the subjects in this study

Characteristic	2016 (*n* = 31)	2018 (*n* = 40)	*P*
Age (years ± SD)	45.58 ± 11.49	51.55 ± 13.55	0.053
Female sex (%)	17 (54.84)	26 (65.00)	0.385
Evolution of the disease (years ± SD)	8.74 ± 3.97	9.15 ± 11.59	0.086
Place of origin			
Europe (%)	24 (77.42)	33 (82.50)	0.593
Northern Africa (%)	1 (3.23)	1 (2.50)	0.855
Latin America (%)	3 (9.67)	4 (10.00)	0.642
Southern Asia (%)	2 (6.45)	1 (2.50)	0.404
South Caucasus (%)	1 (3.23)	1 (2.50)	0.855

SD: standard deviation.

Table 2. Comparison of the numbers of prescriptions filled

Characteristic	2016 *n* = 31	2018 *n* = 40	*P*
Biological drugs			
Anti-TNF-α (%)	25 (80.65)	18 (45.00)	**0.023**
Anti-IL17 (%)	1 (3.22)	2 (5.00)	0.595
Anti-IL12/23 (%)	4 (12.91)	14 (35.00)	**0.034**
Anti-CD28 (%)	0	2 (5.00)	0.313
Anti-IL6 (%)	1 (3.22)	1 (2.50)	0.686
JAK inh (%)	0	3 (7.50)	0.173
Prescribing specialties			
Dermatology (%)	13 (41.90)	19 (47.50)	0.640
GI (%)	4 (12.90)	1 (2.50)	0.089
Rheumatology (%)	14 (45.20)	20 (50.00)	0.685

CD: cluster of differentiation; GI: gastroenterology; IL: interleukin; JAK inh: Janus kinase inhibitor; TNF: tumor necrosis factor.

Table 3. Comparison of the tests performed as part of pre-biological studies

Test	2016 *n* = 31	2018 *n* = 40	*p*
TB screening			
PPD (%)	29 (93.50)	31 (77.50)	0.061
positive (%)	11 (37.90)	0	**< 0.001**
IGRA (%)	3 (9.70)	32 (80.00)	**< 0.001**
positive	0	10 (31.30)	0.461
Chest radiograph (%)	25 (80.60)	33 (82.50)	0.841
ChP indication* for LTI**	11 (35.50)	11 (27.50)	0.470
ChP according to protocol (%)	4 (36.40)	9 (81.80)	**0.040**
HBV blood screening			
HbsAg (%)	24 (77.42)	40 (100.00)	**0.002**
antiHBs (%)	0	40 (100.00)	**< 0.001**
antiHBc (%)	0	40 (100.00)	**< 0.001**
Other blood tests			
antiHCV (%)	24 (77.42)	40 (100.00)	**0.002**
antiHAC (%)	0	39 (97.50)	**< 0.001**
antiHIV (%)	14 (45.16)	40 (100.00)	**< 0.001**
anti-rubella/measles (%)	0	40 (100.00)	**< 0.001**
anti-smallpox (%)	0	40 (100.00)	**< 0.001**

ChP: chemoprophylaxis; HAC: hepatitis A virus; HBc: hepatitis B core antibody; HBs: hepatitis B surface antibody; HbsAg: hepatitis B virus surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; IGRA: interferon-gamma release assay; LTI: latent tuberculosis infection; PPD: Purified protein derivative.

Table 4. Comparative analysis of immunizations

Vaccines	2016 *n* = 31	2018 *n* = 40	*P*
Previous to examination			
PCV13 (%)	0	5 (12.50)	**0.050**
PCV23 (%)	3 (9.68)	7 (17.50)	0.279
After examination			
PnC13 (%)	8 (25.80)	37 (92.50)	**< 0.001**
Pn23 (%)	20 (64.52)	39 (97.50)	**< 0.001**
Influenza (%)	19 (61.29)	25 (62.50)	0.917
HAV, administered/indicated (%)	-	8/8 (100.00)	-
VHB	-	29/30 (96.66)	-
MMR vaccine, administered/indicated (%)	-	2/5 (40.00)	-
Smallpox, administered/indicated (%)	-	1/1 (100.00)	-

HAV: hepatitis A virus; HBV: hepatitis B virus; Pn23: 23-valent pneumococcal polysaccharide vaccine; PnC13: 13-valent pneumococcal conjugate vaccine.

Discussion

The findings of this study show that the creation a BTC committee may result in improvements to healthcare. Previous studies described the responsibilities and functions of the members of a pharmacy and therapeutics committee[10], and the keys to successfully establish one such committee[11]. Nevertheless, we believe this is the first study that shows the usefulness that a BTC or a pharmacy and therapeutics committee could have for clinical practice. It was precisely for that reason that no comparisons could be made with previously published reports.

The chief limitation of this study was our inability to measure the clinical repercussions of the development of the BTC as the number of patients included and the length of follow-up were insufficient to allow identification of any changes in the patients' infection status.

Creation of the BTC has brought about changes in prescription patterns. This is probably due to the fact that the departments involved in managing such drugs were allowed to have their say during the meetings of the committee, which was not the case when decisions about these therapies were adopted by less specific bodies such as the pharmacy and therapeutics committee, the hospital medication committee or the outpatient dispensing committee. What usually happens on these committees is that the member representing all the different medical specialties is an internal medicine specialist, whose daily practice tends to be for the most part unrelated to BDs. It should also be mentioned that the range of therapeutic options –particularly in the realm of dermatology– has experienced such a huge expansion since 2017 that anti-TNFα have been replaced by a whole series of newer drugs.

On the basis of the analyzed data it can be affirmed that the development of the BTC has allowed an improvement in the quality of pre-biological studies, which in the past used to be much less comprehensive. The enhanced understanding by the members of the group of the advantages of BDs and the implementation of an evidence-based protocol containing a definition of the different tests to be performed as part of the pre-biological analysis were crucial elements in making sure that no patient was started on treatment with a BD without having previously undergone a comprehensive analysis. In short, as a result of the establishment of the biological therapies committee every patient came to benefit from appropriate prevention against infection.

In 2016 TB screening only involved a PPD or a IGRA test, the latter being used only in cases where the PPD test was unavailable. As a result of the literature review carried out when setting up the BTC, it was found that the best alternative in the case of immunosuppressed patients was to carry out a dual PPD/IGRA screening[12,13]. Thus is the reason why the establishment of BTC also resulted in higher detection rates of latent tuberculosis infection (LTBI).

No differences were found in other aspects of TB screening or in the number of patients with an indication of chemoprophylaxis for LTBI. However, the number of patients where chemoprophylaxis was performed in strict compliance with the established protocol was significantly higher once the BTC had been set up. In response to the controversy in the literature as to whether chemoprophylaxis should be applied for six or for nine months[12], the committee agreed that all patients should undergo chemoprophylaxis for nine months. Length of prophylaxis in 2016 was shorter than this in all cases.

Moreover, some authors have reported that patient adherence to chemoprophylaxis is suboptimal[14], not only because of its duration but also because the medications are often ill tolerated. Creation of the new BTC also improved adherence to chemotherapy, partly because of the greater awareness of the staff involved.

The committee also promoted changes in the way viral conditions were screened. In 2016 patients were only tested for HCV and HIV antibodies and the HBV surface antigen, if that. In fact, HIV screening was performed in less than half the patients started on biological treatment that year. In 2018, patients were also tested for HAV, rubella, measles and smallpox antibodies, as well as the HBV core and surface antibodies. This shows the extent to which the creation of the BTC resulted in an improvement in the prevention of viral conditions.

Indication and administration of vaccines was also statistically different in the two periods analyzed. As a result of the setting up of the committee, the number of administrations of both the PnC13 and Pn23 vaccines doubled.

Before the committee was established, patients were referred to their outpatient clinic for the vaccines they needed without any involvement of hospital specialists. This changed after the committee agreed that prescription of vaccines should be entrusted to pharmacists, who would be required to follow a specific protocol, and that their administration should be left in the hands of the nursing staff of the pharmacy department. From this moment onward, immunizations came to be fully suited to the needs of each patient.

The creation of a specific BTC has allowed significant improvements in the treatment of IMIDs, as it has contributed to promoting a greater understanding of the drugs used and of how to prevent infection-related adverse events. An awareness by members of the committee of the points of view of colleagues also involved in the use of BDs has resulted in a change in prescription patterns and has increased their understanding of the importance of an appropriate screening for infections of a comprehensive immunization strategy. The pharmacy and therapeutics committee should promote the development of specialized committees like the drug therapies committee.

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Conflict of interests

No conflict of interest.

Contribution to the scientific literature

No data are available regarding the contribution that a biological therapies committee. or any other drug-based committee - could make to a healthcare system. Quantifying the impact of such committees is essential to show their value and to gather the evidence required to advocate for their creation and continuity.

ANNEX 1. Data collection sheet

Patient number: .....

Age: ..... Indication AB: .....

Sex: ..... Country of origin: ..... Specialty: .....

AB: ..... Years of evolution of disease: .....

Was a PPD test performed? ☐ Yes ☐ No

Was an IGRA test performed? ☐ Yes ☐ No If positive: ..... mm

Was a chest x-ray performed? ☐ Yes ☐ No If positive: ..... UI/ml

Was chemotherapy indicated for LTBI? ☐ Yes ☐ No If so, was the chemoprophylaxis protocol followed? ☐ Yes ☐ No

Were the following analyses performed?

		Result, was the indicated action taken? (if positive)
HBsAg	☐ Yes ☐ No	
AntiHBc	☐ Yes ☐ No	..... ☐ Yes ☐ N/A ☐ No
AntiHBs	☐ Yes ☐ No	..... ☐ Yes ☐ N/A ☐ No
If HBsHg i AntiHBc - i AntiHBs < 10 UI/l,		.....
If HBsHg - i AntiHBc +:		Was a vaccine applied? ☐ Yes ☐ No
HBV DNA	☐ Yes ☐ No	
AntiHCV	☐ Yes ☐ No	..... ☐ Yes ☐ No
If AntiHCV +:		.....
HCV RNA	☐ Yes ☐ No	
IgG HAV	☐ Yes ☐ No	..... ☐ Yes ☐ N/A ☐ No
If IgG HAV - :		.....
AntiHIV	☐ Yes ☐ No	Was a vaccine applied? ☐ Yes ☐ No
If antiHIV+:		
HIV RNA	☐ Yes ☐ No	.....
rubella ab	☐ Yes ☐ No	..... ☐ Yes ☐ N/A ☐ No
chickenpox ab	☐ Yes ☐ No	..... ☐ Yes ☐ No
measles ab	☐ Yes ☐ No	
If rubella/measles/chickenpox -: was a vaccine applied?	☐ Yes ☐ No	

Was a vaccine applied at the time of the exam? ☐ Yes ☐ No

If so, what vaccine was applied? .....

¿Was the PnC13 vaccine administrated? ☐ Yes ☐ No

Was the Pn23 vaccine administrated? ☐ Yes ☐ No

Was the influenza vaccine administrated? ☐ Yes ☐ No

*N/A: not applicable.

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