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Assisted therapy model for dispensing immunobiological drugs for rheumatoid arthritis by the Brazilian Unified Health System: rational use of resources reduces expenses

Modelo de terapia assistida para dispensação de medicamentos imunobiológicos para artrite reumatoide no Sistema Único de Saúde: uso racional de recursos reduz despesas

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rheumatoid arthritis, immunobiological agents, cost, rational use, economy

ABSTRACT

Objective: The incorporation of immunobiological agents for rheumatoid arthritis (RA) treatment at the Brazilian Unified Health System (SUS) represented a significant advance but had an important impact on the budget. As the current model of direct patient delivery had deficiencies, the CEDMAC model of assisted therapy was implemented to focus on rational use to minimize expenses and increase access. However, there is no data to compare the two models. Thus, this study aimed to compare the number of bottles effectively dispensed by the CEDMAC model to direct dispensing and assess its financial impact. **Methods**: Care of RA patients at CEDMAC in 2015, whose immunobiological drugs were provided by the Ministry of Health, were included. Drug and dose received, prescribed dose, the number of bottles, cancellations due to contraindication, and absences were recorded. As a comparison, the number of bottles that would be delivered by direct dispensing was estimated. The difference between the total number of bottles dispensed by the two systems and the financial impact of the purchase price in 2015 was calculated. **Results**: In 2015, CEDMAC provided 3,784 consultations for RA patients. The total number of bottles of immunobiological agents prescribed was 10,000 bottles, and 1,946 (19.5%) were not used for bottle optimization, contraindications, or absenteeism. Unused bottles reduced expenses by R$ 806,132.62. The expansion of the model to the entire SUS would reduce costs by R$ 121,110,388.27. **Conclusion**: The CEDMAC assisted therapy model considerably reduces the volume of dispensed bottles and can significantly reduce expenses in the supply of immunobiological agents for RA at SUS.

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RESUMO

Objetivo: A incorporação dos imunobiológicos para tratamento da artrite reumatoide (AR) no Sistema Único de Saúde (SUS) representou um avanço significativo, porém teve um impacto importante no orçamento. Como o modelo vigente de dispensação direta ao paciente apresentava deficiências, implementou-se o modelo do CEDMAC de terapia assistida com foco no uso racional, visando minimizar despesas e potencializar o alcance. Entretanto, não há dados que comparem os dois modelos. Assim, esse estudo objetivou comparar o número de frascos efetivamente dispensados pelo modelo do CEDMAC à dispensação direta e avaliar seu impacto financeiro. **Métodos:** Foram incluídos atendimentos de pacientes com AR no CEDMAC em 2015, cujo imunobiológico foi fornecido pelo Ministério da Saúde. Foram registrados medicamento e dose recebidos, dose prescrita, número de frascos, cancelamentos por contraindicação e faltas. Como comparação, foi estimado o número de frascos que seriam entregues pela dispensação direta. Calculou-se a diferença entre o número total de frascos dispensados pelos dois sistemas e o impacto financeiro pelo valor de aquisição em 2015. **Resultados:** Em 2015, o CEDMAC realizou 3.784 atendimentos para pacientes com AR. O total de frascos de imunobiológicos prescritos foi de 10.000 frascos e 1.946 (19,5%) não foram utilizados por otimização de frascos, contraindicações ou absenteísmo. Os frascos não utilizados reduziram as despesas em R$ 806.132,62. A expansão do modelo para todo SUS reduziria as despesas em R$ 121.110.388,27. **Conclusão:** O modelo de terapia assistida do CEDMAC reduz consideravelmente o volume de frascos dispensados e pode trazer uma relevante redução de despesas no fornecimento dos imunobiológicos para AR no SUS.

Introduction

The incorporation of immunobiological drugs for rheumatoid arthritis (RA) treatment within the scope of the Brazilian Unified Health System (SUS) was a significant advance (Brazil, 2002). RA is a chronic inflammatory disease that affects around 1% of the population and mainly affects the joints of hands and feet, leading to severe functional limitation due to the destruction of joint structures during the disease course (Mota, 2012). Treatment primarily consists of attempting to control this inflammatory process in a sustained manner (Smolen, 2017). Several therapeutic options have been used throughout history to control inflammation and, consequently, the disease progression, initially with synthetic molecules and, more recently, with targeted therapies, constructed through genetic engineering and called generically immunobiological agents (Strand, 2007). These new technologies collaborated to change the natural course of the disease in refractory patients to the traditional treatment and contributed to reducing the patients' disability and providing a better quality of life for this population (Mota, 2012). On the other hand, access expansion to these high-cost drugs began to consume a considerable part of the public budget due to the progressive increase in the volume of dispensations over the years.

Therein, the rational use of immunobiological agents could minimize waste and potentiate the number of patients treated. However, the current predominant model of direct dispensing to the patient weakens the storage chain and drugs transport and leaves a critical gap in application safety and in ensuring the best allocation of resources. Considering that all immunobiological agents included for the treatment of RA are thermolabile and injectable (subcutaneous or intravenous), the current system does not seem ideal.

To fill this gap, it was created the Center for Dispensing High-Cost Medications (CEDMAC) in 2007, a partnership between the Rheumatology Discipline of the *Faculdade de Medicina da Universidade de São Paulo* (FMUSP) [the University of São Paulo Medical School] and the *Secretaria de Estado de São Paulo* [São Paulo Health State Department] with the support from the *Fundação de Amparo à Pesquisa do Estado de São Paulo* [Foundation for Research Support of the São Paulo State]. They proposed establishing a new model for managing immunobiological agents in Rheumatology based on assisted therapy and a focus on safety, rationalization of use, and combating waste.

In the CEDMAC model, all the logistics related to the medication do not depend on direct contact with the patient. Transport and storage are carried out by institutions involved in the process with the recommended control. For applications, only scheduled appointments are performed, following a protocol developed by CEDMAC. The attendance is multidisciplinary and involves a medical, nursing, pharmaceutical, and administrative team. The care protocol includes systematic tracking of possible contraindications to the application, assisted application under medical supervision to deal with any immediate adverse reactions, and effectiveness control, in addition to an active search for absent patients, promoting treatment adherence. The assisted application also allows the sharing of intravenous medication bottles with a dose per kilogram of weight, leading to a reduction in waste and optimization of resources by treating a higher number of patients with the same number of bottles. For subcutaneously applied medications, the assisted therapy avoids dispensing for patients with specific contraindications, increasing the safety of the treatment and preventing the accumulation of bottles in possession of patients in cases

of applications postponement. This process contrasts with the direct dispensing system, which delivers monthly doses regardless of whether the patient has already used the previously dispensed doses.

Notwithstanding the potential advantages of the CEDMAC assisted therapy model, so far, there is no data to prove and quantify its superiority to the predominant model of direct dispensing by SUS regarding the volume of immunobiological agents distributed and the financial impact.

This study evaluates the reduction in the volume of immunobiological drugs for RA dispensed through the CEDMAC assisted therapy model and the financial impact of this volume reduction compared to the direct dispensing model in force within the SUS, in addition to estimating the cost reduction that could be achieved for the acquisition of medicines, if the CEDMAC model of assisted therapy was extended to the entire SUS.

Methods

Evaluated appointments

All patients seen with RA diagnosis, scheduled at CEDMAC from 01/01/2015 to 12/31/2015, whose medication was provided by the Ministry of Health, were included.

Immunobiological drugs

The immunobiological drugs used included in the specialized component of pharmaceutical care list of the Ministry of Health for RA: abatacept, adalimumab, etanercept, golimumab, infliximab, rituximab, and tocilizumab (Table 1).

Comparison between assisted therapy and direct dispensing models

Appointments at CEDMAC were recorded for each patient according to the medication and dose received, prescribed dose, number of bottles, cancellations due to contraindication, and absences. As a comparison, the number of bottles dispenses for each patient was estimated if the system was for direct dispensing.

Patients who started or stopped treatment during the study period had their estimates adjusted proportionally to the time of medication use.

Data were aggregated, and the reduction in volume dispensed was calculated by the difference between the total number of bottles estimated by direct dispensing subtracted from the number of bottles effectively used.

The number of additional treatments that could be performed using the volume of bottles saved was also estimated. For each drug, the number of bottles saved was divided by the average number of bottles used for each treatment, thus finding the number of possible additional treatments using the total number of optimized bottles.

Financial estimate

The financial value in reais referring to the volume reduction by the CEDMAC model was calculated by multiplying the amount saved for each drug by the unit purchase price of each immunobiological drug by the Ministry of Health in 2015, shown in Table 2 (Brazil, 2017).

Table 2. Unit values for the acquisition of immunobiological drugs available in the specialized component of pharmaceutical assistance of the Ministry of Health in 2015

Medication	Acquisition value (R$)
Abatacept 250 mg	412.54
Adalimumab 40 mg	776.09
Certolizumab 200 mg	466.56
Etanercept 50 mg	381.00
Golimumab 50 mg	1,331.22
Infliximab 100 mg	939.14
Rituximab 500 mg	1,908.48
Tocilizumab 80 mg	180.49

Table 1. The dosage schedule and administration routes of immunobiological drugs for RA according to the Ministry of Health's PCDT in 2015

Medication	Route	Dose	Interval
Abatacept 250 mg	IV	500 mg (<60 kg) 750 mg (60-100 kg) 1.000 mg (>100 kg)	Weeks 0, 2 and 4 and after every 4 weeks
Adalimumab 40 mg	SC	40 mg	2 weeks
Certolizumab 200 mg	SC	400 mg	Weeks 0, 2 and 4 and after every 4 weeks
Etanercept 50 mg	SC	50 mg	Weekly
Golimumab 50 mg	SC	50 mg	4 weeks
Infliximab 100 mg	IV	3 mg/kg body weight	Weeks 0, 2 and 6 and after every 8 weeks
Rituximab 500 mg	IV	1,000 mg	Weeks 0 and 2 every 6 months
Tocilizumab 80 mg	IV	8 mg/kg (maximum dose 800 mg)	4 weeks

IV: intravenous; SC: subcutaneous.

The possible cost-cutting impact of expanding the CEDMAC assisted therapy model to the entire SUS was estimated by extrapolating the reduction in expenses seen in CEDMAC care to the total number of bottles dispensed by the SUS for the diagnosis of RA (CID10 - M05.0, M05.3, M05.8, M06.0, and M06.8) in 2015, according to Datasus, for each immunobiological drug available.

Statistical analysis

The Student's t-test was used to compare the number of bottles values. The prescribed and the used ones for each medication. *P*-values < 0.05 were considered significant.

Results

CEDMAC scheduled 9,139 appointments for patients using immunobiological agents during the study period, with 3,784 for patients diagnosed with RA. The total number of prescribed bottles of all drugs for the treatment of RA was 10,000 bottles, and 1,946 (19.5%) were not used. Table 3 describes the dispensing reduction broken down for each immunobiological drug. Bottle savings were statistically significant for all drugs except rituximab. In the analysis of dispensing reduction, 1,724 bottles saved were attributed to non-application due to contraindication or absenteeism and 222 bottles to optimization resulting from the sharing of bottles. Considering that only infliximab and tocilizumab allow sharing optimization, of the 854 bottles saved for these two drugs, 26% were because of bottle sharing at the time of application.

The number of bottles saved would allow for an additional number of treatments in the order of 20.3%, considerably increasing the system's capacity without adding cost. Table 4 shows the possible other treatments for each drug based on the bottle savings generated by the CEDMAC model.

In financial terms, unused bottles corresponded to an expense reduction of R$ 806,132.62, equivalent to 17.7% of the total prescribed value (Table 5).

If this model is expanded to the entire SUS, expenses reduction could be R$ 121,110,388.27 in values at the time, based on the total volume of units of each immunobiological

Table 3. Comparison of the prescribed and effectively used volume for each immunobiological drug in the CEDMAC model of the assisted application in 2015

Medication	Treatments (n)	Bottles prescribed (n)	Bottles used (n)	Saved volume (n)	Saved volume (%)	P
Abatacept 250 mg	96	2,553	2,177	376	14.7	<0.001
Adalimumae 40 mg	24	488	390	98	20.1	<0.001
Certolizumab 200 mg	14	217	174	43	19.8	<0.001
Etanercept 50 mg	49	1,944	1,658	286	14.7	<0.001
Golimumab 50 mg	20	165	128	37	22.4	<0.001
Infliximab 100 mg	32	696	505	191	27.5	<0.001
Rituximab 500 mg	63	398	368	30	7.5	0.08
Tocilizumab 80 mg	55	3,539	2,654	885	25.0	<0.001

Table 4. Estimate of possible additional treatments using the volume saved for each immunobiological drug in the CEDMAC model of the assisted application in 2015

Medication	Saved volume (n)	Average of bottles used per treatment (n)	Other possible treatments (n)	Treatments performed (n)	Other possible treatments (%)
Abatacept 250 mg	376	22.7	16	96	16.7
Adalimumab 40 mg	98	16.3	6	24	25.0
Certolizumab 200 mg	43	12.4	3	14	21.4
Etanercept 50 mg	286	33.8	8	49	16.3
Golimumab 50 mg	37	6.4	5	20	25.0
Infliximab 100 mg	191	15.8	12	32	37.5
Rituximab 500 mg	30	5.8	5	63	7.9
Tocilizumab 80 mg	885	48.3	18	55	32.7

drug dispensed for RA by the Ministry of Health, according to Datasus, in 2015. The percentage reduction of dispensed bottles generated by the CEDMAC model was extrapolated to Datasus data to estimate the reduction of expenses in SUS, as shown in Table 6.

Discussion

This paper is the first study to quantify the savings of bottles of immunobiological medications dispensed for RA by an assisted therapy model compared to the current model of direct dispensing to the patient predominant in SUS.

This data is relevant since RA is a chronic inflammatory disease that, as a rule, is treated for extended periods because, in the absence of treatment, the disease tends to reactivate. Thus, patients who cannot adequately control it with the traditional treatment and need to start immunobiological drugs will use them for a long time.

It is estimated that 30% of patients with RA will be indicated for immunobiological drugs for proper control of their disease. This number, associated with prolonged use and the fact that immunobiological agents are expensive, significantly impacts the SUS budget for the supply of these drugs.

On the other hand, incorporating these drugs into the SUS significantly advanced the therapeutic arsenal against RA. Immunobiological drugs have been shown to reduce the chance of these patients progressing to functional loss due to structural joint damage and, thus, contribute to less disability and less product loss in this population.

Thus, the supply of immunobiological drugs by the SUS must be done efficiently based on rational use and combating waste to impact the system's sustainability positively. However, what is observed in practice is that the current predominant model of access to biological medicines at SUS by direct dispensing to the patient is deficient in several aspects.

First, medicines are delivered directly to patients, risking their proper conservation, as they are thermolabile products

Table 5. Financial comparison of the amount prescribed and effectively used, for each immunobiological drug, in the CEDMAC model of the assisted application in 2015

Medication	Amount prescribed (R$)	Amount used (R$)	Generated savings (R$)	Generated savings (%)
Abatacept 250 mg	1,053,215.00	898,099.60	155,115.40	14.7
Adalimumab 40 mg	378,731.90	302,675.10	76,056.80	20.1
Certolizumab 200 mg	101,243.50	81,181.44	20,062.06	19.8
Etanercept 50 mg	740,664.00	631,698.00	108,966.00	14.7
Golimumab 50 mg	219,651.30	170,396.20	49,255.10	22.4
Infliximab 100 mg	653,641.40	474,030.90	179,610.50	27.5
Rituximab 500 mg	759,575.00	702,320.60	57,254.40	7.5
Tocilizumab 80 mg	638,663.90	478,851.30	159,812.60	25.0
Total 2015	**4,545,386.00**	**3,739,253.14**	**806,132.86**	**17.7**

Table 6. Estimated cost reduction in the supply of immunobiological drugs for RA in the hypothesis that the CEDMAC model of assisted therapy is disseminated within the SUS in 2015

Medication	Amount dispensed (R$)	Estimated savings (%)	Potential savings amount (R$)
Abatacept 250 mg	21,904,223.84	14.7	3,219,920.90
Adalimumab 40 mg	261,362,277.10	20.1	52,533,807.65
Certolizumab 200 mg	8,525,450.88	19.8	1,688,039.27
Etanercept 50 mg	214,365,840.00	14.7	31,511,778.48
Golimumab 50 mg	55,293,553.92	22.4	12,385,756.08
Infliximab 100 mg	44,094,501.28	27.5	12,125,987.85
Rituximab 500 mg	15,739,234.56	7.5	1,180,442.59
Tocilizumab 80 mg	25,858,621.81	25.0	6,464,655.45
Total 2015	**647,143,703.39**	**18.7**	**121,110,388.27**

and require specific storage and transport conditions that guarantee their quality. In addition, the available immunobiological drugs are injectable, requiring a healthcare structure for application, especially for the intravenous route, which the current model does not cover.

Another concern is the application itself. These medications may present contraindications at the application that may not be observed or noticed by patients who perform self-application, in the case of subcutaneous medicines, increasing the risk of adverse events. In addition, intravenous medications such as infliximab and tocilizumab have a standard dose by patient weight, leading to drug disposals when the entire bottle is not used. A final aspect about fixed dispensing, regardless of whether the patient has had the last dose or not, results in waste to the chain and drug storage outside the system.

The development of the CEDMAC assisted therapy model brought solutions to all these issues, taking the direct interaction of the patient with immunobiological drugs as a premise. The patient's access to the medication is guaranteed, and a multidisciplinary team checks possible contraindications before each application. The bottles are stored, following the safety and transport recommendations, in the institution itself, and, as a rule, the excess doses of medications by weight are shared, making drug disposal exceptional. Only the drug used is dispensed, preventing the storage of medicines outside the system, increasing efficiency, and rationalizing use. Also, the CEDMAC model monitors treatment effectiveness through a structured protocol in electronic medical records, allowing for in-depth analysis of the generated data.

Saving drugs by the CEDMAC model can be analyzed in two main ways. The first concerns the reduction of expenses itself, which would allow other uses for these public resources within the health system or even allow the incorporation of new technologies still absent from the Ministry of Health protocols. The second analysis will enable us to infer that the economy achieved in dispensing increases system capacity considerably, without adding expense, expanding population reach, as demonstrated by the number of additional treatments possible from the savings brought about by the CEDMAC model.

In this sense, the question arises about the investments needed to implement an assisted therapy network that could serve the entire public system and fund the model. This estimate was not part of the scope of this study. However, in theory, significant investments would not be necessary, as the SUS already has a capillary network of the national vaccination program's cold chain that could be used to transport and store immunobiological drugs. The adequate physical structure is not very complex, and the necessary personnel (nursing, medical team, and pharmacy) could be trained at a low cost in existing reference centers. In the case of intercurrence and complications, the support of regional reference hospitals would be established.

A possible limitation of this study is that the Hospital das Clínicas of FMUSP is a tertiary service with a population with RA that is probably more severe than the country average, making the extrapolation of the data reported here uncertain. At this point, it is noteworthy that the unit cost of acquisition of immunobiological drugs has been dropping over time. Hence, the survey of the estimate of public resources saved in this study only contributes to viewing what happened in 2015 but cannot be extrapolated to the present time, even with the growing demand for the dispensing of immunobiological agents.

On the other hand, the current study presents some advantages that corroborate its importance. It is the first study that makes this type of analysis comparing an assisted therapy model to the predominant direct dispensing model in SUS. The CEDMAC model has already been in full operation for 12 years, and it can be said that it is already tested and consolidated as an alternative. A relevant number of patients and consultations was evaluated, which increases the strength of the data obtained. And finally, the knowledge acquired over time and described in this study can serve as the basis for an expansion and multiplication project of the CEDMAC assisted therapy model within the SUS.

Conclusion

The data presented suggest that the assisted therapy model currently used at CEDMAC considerably reduces the number of bottles of immunobiological drugs dispensed, compared to the predominant model of direct patient delivery, and can bring relevant savings in the supply of these drugs for RA in the SUS.

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