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## REFERÊNCIA

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# How long does it take to translate research findings into routine healthcare practice? – the case of biological drugs for rheumatoid arthritis in Brazil

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**Background:** The literature reports long time lags between the several processes involved in the translation of drug research and development into clinical application. To expedite these processes, translational research has emerged as a process that can be applied to reduce the lag between scientific discoveries and their practical application. Thus, the objective of this study was to estimate the time lag in translational research of biological drugs for the treatment of rheumatoid arthritis included in the Brazilian Unified Health System [*Sistema Único de Saúde (SUS)*].

**Methods:** A descriptive retrospective study was conducted based on secondary data loaded by SUS users in public sources and systems to estimate the time lag between the publication of phase I clinical trial results to drug use in clinical settings. The dates of translational research activities were identified from markers and steps. Structured searches were conducted in the literature and reports from the National Commission for the Incorporation of Technologies in the SUS (Conitec) as well as from health authorities, and analyzed.

**Results:** Between 2012 and 2019, SUS included five biological agents for the treatment of rheumatoid arthritis. The mean time lag from clinical development to use of these agents was 11.13 years (range, 8.57 to 12.90 years). The mean time lag for the stages of translational research were 5.30 (T1—basic research to clinical research), 5.08 (T2—clinical research to research synthesis), and 0.75 (T3—research synthesis to evidence-based practice) years. A shorter time lag was observed in the Brazilian case when it was possible to compare with other studies.

**Conclusions:** The estimated time lag of biological drugs used in the treatment of rheumatoid arthritis was determined based on the translational research steps model adapted to the Brazilian context. Brazil has instituted legal frameworks that set deadlines for sanitary registration, health technology assessment (HTA), and the availability of drugs in the SUS, thus, allowing for a reduced stage T2 time lag. Nevertheless, improvements are still required in stages T1 and T2, especially in publishing the results of clinical trials.

**Keywords:** Translational medical research; biological products; rheumatoid arthritis; health policy; unified health system

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## Introduction

The time lag between drug research and development and ultimate translation into healthcare practice is still a major barrier to health care access in different contexts (1,2). The time lag from the initial drug discovery to identifying a therapeutic target or receptor for drug development and then final registration or market authorization of a dosage form has been estimated to take 17 (3), 22 (4), or even 36 years (1). Owing to this, translational research seeks to reduce the time gap between obtaining data for research and practical use of the acquired knowledge for the benefit of society (5-7). Translational research allows the identification of strategies and actions to integrate the steps and stakeholders involved in order to optimize the drug development processes and thus provide access to therapeutics (8).

Rheumatoid arthritis is a systemic and progressive autoimmune disease clinically characterized by joint pain and swelling. Owing to its chronic and complex inflammatory nature, several comorbidities and extra-articular presentations can develop, the most common being cardiovascular complications, respiratory diseases, and infections (9,10). In addition to clinical consequences, the socioeconomic impacts of rheumatoid arthritis, such as functional disability, poor quality of life, loss of productivity, and high individual and collective healthcare costs are also a cause for concern (11). Estimates from the 2017 Global Burden of Disease (GBD) study showed an age-standardized global prevalence and incidence of 246.6 and 14.9 per 100,000 in that year, which corresponded to increases of 7.4% and 8.2% compared to 1990, respectively (12). Clinical guidelines recommend early diagnosis and treatment (13-15) as delayed disease management is associated with the worsening of the clinical condition, including pain and loss of quality of life, more erosive joint damage, extra-articular manifestations and increased morbidity and mortality (16-19). In addition, treatment delays are related to higher direct and indirect costs of disease management, as patients fail to achieve better outcomes and negatively impact health systems (11,20).

The treatment of rheumatoid arthritis involves controlling inflammation to attain disease remission or low activity. To this effect, three groups of disease-modifying antirheumatic drugs (DMARDs) are used: conventional synthetic, targeted synthetic, and biological drugs (9,13,14). Biological DMARDs have changed the course of managing rheumatoid arthritis, through increasing treatment

safety and effectiveness and providing better clinical and socioeconomic outcomes (21,22). Nevertheless, even with the advancement of science and the availability of evidence on the pathophysiology, diagnosis, treatment, and prognosis of rheumatoid arthritis, a review of the literature indicated a mean time lag of 11.76 months between symptom onset and treatment initiation (16).

Considering that patients may experience failures to control the disease, it is relevant that physicians and patients have more medicines available promptly to contain the progression of the disease. This could minimize the time lag for switching drugs that have failed to control the disease for others that can provide personalized treatment, with better outcomes. Therefore, knowing the time lag of the translational research process in the context of access to biological drugs for rheumatoid arthritis is important to identify priority strategies to reduce the wait. Accordingly, the objective of this study was to estimate the time lag between the initial phase of clinical development and the dispensing of biological DMARDs incorporated in the Brazilian Unified Health System for the treatment of rheumatoid arthritis.

## Methods

### *Research context*

To ensure provision of adequate healthcare in a country with large socioeconomic and health inequalities, the 1988 Constitution of the Federative Republic of Brazil established a public, universal, and free health system at the point of service called the Unified Health System [*Sistema Único de Saúde* (SUS)] (23,24). In addition, the National Health Policy of this system encompasses several sectorial policies, including drugs and pharmaceutical services, and establishes guidelines for free access and rational drug use. Prior to their inclusion as part of the SUS medicines, drugs must be authorized for use in the Brazilian market after approval by the Brazilian Health Regulatory Agency [*Agência Nacional de Vigilância Sanitária* (Anvisa)], a health regulator linked to the Ministry of Health. According to legislation, the drugs must be registered with Anvisa and should undergo evaluation by the National Commission for the Incorporation of Technologies in the SUS [*Comissão Nacional de Incorporação de Tecnologias no SUS* (Conitec)] before being included as part of the SUS. Having fulfilled these requirements, it is up to the Ministry of Health to decide whether to adopt a new treatment into the SUS. Since 2012, the Conitec evaluation requires that it be conducted within 180 days, extendable

for 90 days, and considers efficacy, safety, effectiveness, cost-effectiveness, and budget impact criteria. After a possible inclusion decision, the provision of the drugs must occur within 180 days of the decision date and is guided by clinical guidelines (25,26). The drugs can be purchased directly by the Ministry of Health or by States and municipalities, as agreed between SUS managers. Clinical guidelines are used as tools to help manage and regulate access to health technologies, and include clinical indications, dosages, monitoring mechanisms, and parameters related to drug dispensing and clinical management (27).

### *Research design*

The study had a descriptive, retrospective design, with secondary public data collection to estimate the time lag between the clinical development of drugs and their dispensing by the SUS, considering the various stages of translational research. The dates of events that made it possible to estimate the time course of the drugs in the context of translational research were identified within the Brazilian scenario.

In addition to a structured literature search in medical literature databases, the study included a documental analysis of recommendation reports and clinical guidelines issued by Conitec, drug registration reports issued by health authorities [Food and Drug Administration (FDA), European Medicines Agency (EMA), and Anvisa], and normative acts issued by the Ministry of Health of Brazil.

The sample consisted of all biological drugs used for the treatment of rheumatoid arthritis evaluated by Conitec between 2012 and 2019 and incorporated into the SUS. The data were collected for each drug to identify the dates on which the events described below occurred.

### *Variables and data sources*

Translational research steps and corresponding markers previously identified in a review that investigated translational drug research models, steps, and stakeholders in the Brazilian context were used (28). Three stages of translational research were defined as follows: T1—from basic research to clinical research; T2—from clinical research to research synthesis; and T3—from research synthesis to evidence-based practice. In each one, markers associated with the dates of certain events were identified. *Table 1* shows the steps, markers, event definitions, and data sources. It should be noted that the

data collected for each marker refers to the date on which a particular event occurred.

The data were collected from several sources described below, with assumptions being adopted to infer the date of each activity. The date of result publications in scientific journals or the date of result availability on the clinical trial registration platform were used as a parameter to infer the conclusion of phase I, II, and III clinical trials. With both pieces of information, the oldest date was included.

To collect the date of publication of clinical trial and systematic review results, a sensitive search strategy was developed for each drug, aiming at retrieving a greater number of documents from the Medline (via PubMed) and ClinicalTrials.gov databases. The Drugbank (29) database was used to identify terms and codes for each molecule. Data sources and search strategies are available as supplementary information ([Appendix 1](#)).

The date of the first health registration of the drug was obtained from the Anvisa, FDA, and EMA websites. The Conitec website was used to confirm the dates of the evaluation request, Conitec initial and final deliberations, decision of incorporation by the Ministry of Health, and publication of the clinical guideline (30).

The date of the first drug purchase by the Ministry of Health was retrieved from the Health Price Database, a system maintained by the Ministry of Health for the registration and consultation of information on the public and private purchase of drugs and health products (31). To infer the dispensing date, data from the SUS Outpatient Information System [*Sistema de Informações Ambulatoriais do SUS (SIA/SUS)*] were extracted through the TABNET tab (32). The SIA/SUS stores data on drug dispensing which is accessible via the Specialized Component of the SUS Pharmaceutical Assistance. Each drug is identified as a procedure and has a unique identification code. Dispensing is only allowed with a medical prescription and by filling out a drug request form. The codes of the International Statistical Classification of Diseases and Related Health Problems (ICD-10)-10th Revision and other parameters established in the clinical guideline of the Ministry of Health can be observed. Through the SIA/SUS, the federation units inform the Ministry of Health about the drug units dispensed throughout their territory using a month/year date. For calculation purposes, day 15 was standardized for this event. In addition, the date of the first dispensation registration by any of the 27 Brazilian federation units was taken into account.

**Table 1** Translational research steps, markers, definitions, and data sources

| Step   | Marker (date)                                     | Marker event definition   | Data source                                 |
|--|---|---|---|
| T1—basic research to clinical research           | Phase I   | Publication of the results of the first phase I clinical trial    | Medline (via PubMed);<br>ClinicalTrials.gov |
|  | Phase II  | Publication of the results of the first phase II clinical trial   |   |
|  | Phase III   | Publication of the results of the first phase III clinical trial  |   |
|  | Health registration                               | Approval of the first health registration by Anvisa, FDA, and EMA | Anvisa; FDA; EMA                            |
| T2—clinical research to research synthesis       | Systematic review                                 | Publication of the first review with systematic search            | Medline (via PubMed)                        |
|  | Conitec request                                   | Assessment request from Conitec                                   | Conitec recommendation report               |
|  | Conitec recommendation                            | Conitec initial recommendation                                    |   |
|  | Conitec deliberation                              | Conitec final decision  |   |
|  | Decision  | Ministry of Health decision                                       |   |
| Conitec guideline                                | Guideline, manual, guide, or protocol publication | Conitec website   |   |
| T3—research synthesis to evidence-based practice | Acquisition                                       | Registration of the first purchase after incorporation            | Ministry of Health Price Database           |
|  | Dispensation                                      | First dispensing record   | SIA/SUS                                     |

Source: Own conception using the dates of translational research activities. Anvisa, Brazilian Health Regulatory Agency; Conitec, National Commission for the Incorporation of Technologies in the SUS; EMA, European Medicines Agency; FDA, Food and Drug Administration; SIA/SUS, SUS Outpatient Information System; SUS, Brazilian Unified Health System.

### Statistical analysis

Descriptive statistics were used to calculate the total and mean time lags between the clinical development and SUS dispensing stages. Microsoft Excel 2019 software was used to calculate the estimates and prepare tables and figures with a schematic representation of the total time and step time for each drug. As the variables of each event were “dates”, the time interval was calculated by subtracting the date of the marker immediately after the date of the previous marker, according to the equation: Time (in months) = Date (marker 2) – Date (marker 1).

### Ethical aspects

Approval by an ethics committee is not applicable as this research used secondary data available in the public domain.

### Results

The study included five biological DMARDs: abatacept, certolizumab, golimumab, rituximab, and tocilizumab. These were all evaluated within the scope of the Conitec

recommendation report no. 12/2012 and incorporated into the SUS through Ordinance SCTIE/MS no. 24/2012, published on 9/11/2012. Some common characteristics of the drugs refer to high unit price, centralized acquisition by the Ministry of Health, need for refrigerated storage, and subcutaneous or intravenous administration (*Table 2*). All dates of events related to markers and translational research steps are available as supplementary information (*Appendix 2*).

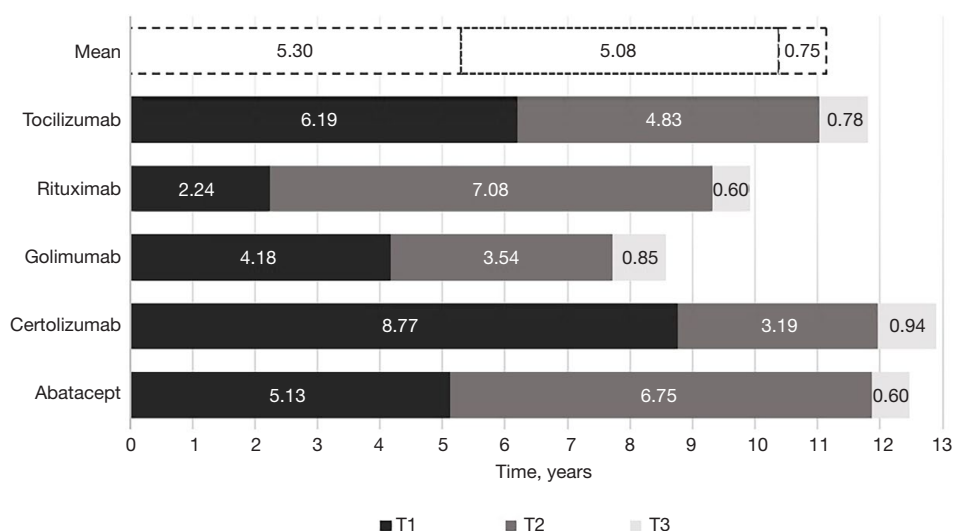
The mean time lag (years) at each stage of the translational research of the five biological drugs was 5.30 for T1, 5.08 for T2, and 0.75 for T3 (*Figure 1*). Added together, the total mean lag was 11.13 years from the publication of the results of phase I clinical trials to the first SUS dispensing. The longest time lag corresponded to the T1 stage, relating to the clinical development of the drug, which comprises phase I, II, and III clinical trials, as well as the registration evaluation by the health authority.

The total time lag (in years) for each drug was as follows: 12.90 for certolizumab; 12.48 for abatacept; 11.80 for tocilizumab; 9.93 for rituximab, and 8.57 for golimumab. Certolizumab, golimumab, and tocilizumab had a longer time course at T1, with abatacept and rituximab having

**Table 2** Information on the five biological DMARDs incorporated into the SUS during the 2012–2019 period

| Drug                                       | Developer country <sup>i</sup> | Class <sup>ii</sup> | Indication <sup>iii,t</sup>   | Dosage (initial dose and maintenance dose) <sup>iii,t</sup>   | Anvisa/FDA/EMA health registration date <sup>v</sup> | Number of annual treatment units <sup>iii</sup> | Maximum regulated price (US\$ PPP) <sup>v,s</sup> | Purchase price (US\$ PPP) <sup>v,s</sup> | Price per treatment/year (US\$ PPP) <sup>v,s</sup> |
|--|--------------------------------|---------------------|---|---|--|---|---|--|--|
| Abatacept 250 mg injection solution powder | USA                            | Not an anti-TNF     | Second stage of treatment, associated with synthetic DMARDs                                 | 750 mg, IV, in weeks 0, 2, and 4. After, 750 mg every 4 weeks | 6/25/2007; 12/23/2005; 5/21/2007                     | 42  | 661.44  | 148.72                                   | 6,246.12   |
| Certolizumab 200 mg/mL injection solution  | Belgium                        | Anti-TNF            | Second stage of treatment, associated with synthetic DMARDs                                 | 400 mg, SC, in weeks 0, 2, and 4. After, 400 mg every 4 weeks | 5/23/2011; 5/13/2009; 10/01/2009                     | 24  | 309.62  | 191.79                                   | 4,602.88   |
| Golimumab 50 mg injection solution         | USA                            | Anti-TNF            | Second stage of treatment, associated with synthetic DMARDs                                 | 50 mg, SC, every 4 weeks                                      | 4/11/2011; 4/24/2009; 10/01/2009                     | 12  | 1457.42   | 451.02                                   | 5,412.19   |
| Rituximab 500 mg injection solution        | Switzerland                    | Not an anti-TNF     | Second stage of treatment, associated with synthetic DMARDs. Reserved for biological DMARDs | 1 g, IV, on days 0 and 14. Repeat every 6 months              | 7/03/2006; 2/28/2006; 9/29/2006                      | 8   | 1471.94   | 423.37                                   | 3,386.93   |
| Tocilizumab 80 mg injection solution       | Switzerland                    | Not an anti-TNF     | Second stage of treatment, associated with synthetic DMARDs                                 | 8 mg/kg, IV, every 4 weeks                                    | 1/19/2009; 1/08/2010; 1/15/2009                      | 84  | 237.68  | 69.75                                    | 5,859.02   |

Source: own conception using the following databases: <sup>i</sup>, drug developer's website; <sup>ii</sup>, product package insert available on Anvisa's website (33); <sup>iii</sup>, clinical guideline of rheumatoid arthritis and juvenile idiopathic arthritis in Brazil (34); <sup>iv</sup>, respective agencies' websites; <sup>v</sup>, website of the CMED (35). The lowest Maximum Selling Price to the government was adopted, at a rate of 17%. When the price referring to the 17% rate was unavailable, the lowest price without rate was adopted; <sup>vi</sup>, Health Price Database website (31). <sup>vii</sup>, the number of pharmaceutical units used per year was multiplied by the price charged by the Ministry of Health. The Brazilian clinical guideline recommends a synthetic DMARD, preferably methotrexate, as the first step in the treatment of rheumatoid arthritis. Biological DMARDs are recommended after failure to at least two therapeutic regimens in the first stage for at least three months each, and with persistent disease activity. <sup>t</sup>, the price of the last purchase made by the Ministry of Health in the period from 01/01/2020 to 10/01/2021 was used; <sup>†</sup>, for calculation purposes, the following were considered: (f) total number of pharmaceutical units used for the initial and maintenance phases of drug treatment; (ll) adult weighing 70 kg. <sup>§</sup>, correction factor applied to PPP (36). DMARDs, disease-modifying antirheumatic drugs; SUS, Brazilian Unified Health System; Anvisa, Brazilian Health Regulatory Agency; FDA, Food and Drug Administration; EMA, European Medicines Agency; PPP, purchasing power parity; TNF, tumor necrosis factor; IV, intravenous; kg, kilograms; mg, milligrams; mL, milliliters; SC, subcutaneous; CMED, Medicine Market Regulation Chamber.



**Figure 1** Time course of the five biological DMARDs during stages of translational research. Stage 1 (T1) has as initial and final markers the publication of the first clinical trial of phase 1 and the registration by Anvisa, respectively. Stage 2 (T2) starts from the first systematic review until the publication of the practice guideline; stage 3 (T3), from the medicines acquisition to its dispensation in the SUS. Source: Own conception using the dates of translational research activities. DMARDs, disease-modifying antirheumatic drugs; Anvisa, Brazilian Health Regulatory Agency; SUS, Brazilian Unified Health System.

longer durations at T2. The longest and shortest lags at T1 were for certolizumab (8.77 years) and rituximab (2.24 years). At T2, the lag for rituximab was 2.2 times longer than for certolizumab, which had the shortest lag in that stage. T3 was very similar for all drugs, being shorter than one year. The lag of the three steps for golimumab (8.57 years) was shorter than the T1 lag for certolizumab (8.77 years).

Table 3 shows the time lag between the markers of the three translational research stages. As for T1, the longest lag occurred between phase III and II clinical trials, with certolizumab totaling 74 months (6.17 years). No publications were found with phase I results for certolizumab and abatacept, which made the first calculation unfeasible. Rheumatoid arthritis was included as a new indication for rituximab before the publication of phase III results, which resulted in a negative time lag. For tocilizumab, the calculation corresponded to 0, as the results of phase II and I studies were available in only one publication. Negative time lags indicate that certain events occurred before another marker.

At stage T2, with the exception of rituximab, all drugs were registered with Anvisa on dates subsequent to the publication of the first identified systematic review, resulting in a negative time lag. The longest lags were

between requesting the demand for an assessment from Conitec and the publication of the first systematic review. These periods corresponded to 55% of the total time lag in T2 for certolizumab and 81% for abatacept. The time lag for abatacept was three times longer than for certolizumab. More homogeneous time lags were found in T3, with a longer period between the acquisition and incorporation decisions than between dispensing and acquisition.

## Discussion

### *Time lags in translational research and their implications*

This study evaluated the mean time lag in three stages of translational research for biological DMARDs, abatacept, certolizumab, golimumab, rituximab, and tocilizumab, included in the SUS following Conitec recommendations in 2012. Added together, the total mean time lag was 11.13 years from the publication of the results of phase I clinical trials to the first SUS dispensing. The longest total time lag was 12.90 years for certolizumab and the lowest was 8.57 years for golimumab. At each stage, the determined mean time lags (years) were 5.30 for T1, 5.08 for T2, and 0.75 for T3. At T1, the longest time lag was between the publication of phase III and II results, while at T2 it was between the publication of the first systematic

**Table 3** Time lag between translational research markers for the five biological drugs

| Step | Marker                                      | Drugs (time lag in months) |                |                 |           |                |
|------|---|----------------------------|----------------|-----------------|-----------|----------------|
|      |   | Anti-TNF                   |                | Not an anti-TNF |           |                |
|      |   | Certolizumab               | Golimumab      | Abatacept       | Rituximab | Tocilizumab    |
| T1   | Phase II-Phase I                            | N/F                        | 13.1           | N/F             | 22.7      | 0 <sup>†</sup> |
|      | Phase III-Phase II                          | 74.0                       | 8.6            | 17.5            | 4.2       | 53.4           |
|      | Health registration-Phase III               | 31.2                       | 28.4           | 44.0            | -0.2      | 20.9           |
| T2   | Systematic review-Health registration       | -12.7                      | -14.9          | -7.9            | 39.7      | -2.8           |
|      | Conitec request-Systematic review           | 21.0                       | 29.4           | 65.3            | 31.7      | 44.4           |
|      | Conitec recommendation-Conitec request      | 4.2                        | 0 <sup>‡</sup> | 2.6             | 0.5       | 0.5            |
|      | Conitec deliberation-Conitec recommendation | 1.1                        | 1.1            | 1.1             | 1.1       | 1.1            |
|      | Decision-Conitec deliberation               | 2.3                        | 2.3            | 2.3             | 2.3       | 2.3            |
|      | Conitec guideline-Decision                  | 9.7                        | 9.7            | 9.7             | 9.7       | 9.7            |
|      | Acquisition-Decision                        | 4.7                        | 7.5            | 4.7             | 5.9       | 8.3            |
| T3   | Dispensation-Acquisition                    | 6.6                        | 2.7            | 2.5             | 1.3       | 1.0            |

Stage 1 (T1) has as initial and final markers the publication of the first clinical trial of phase 1 and the registration by Anvisa, respectively. Stage 2 (T2) starts from the first systematic review until the publication of the practice guideline; stage 3 (T3), from the medicines acquisition to its dispensation in the SUS. <sup>†</sup>, phase I and II clinical trial results published in only one scientific article; <sup>‡</sup>, according to Conitec Recommendation Report No. 12/2012 (30), the company that holds the registration of golimumab requested Conitec to evaluate the drug for incorporation into the SUS on 6/21/2012. This date is after the recommendation date of the aforementioned report (6/1/2012). Conitec decision was on 7/5/2012, while the incorporation decision was on 9/11/2012. TNF, tumor necrosis factor; N/F, not found; Conitec, National Commission for the Incorporation of Technologies in the SUS; Anvisa, Brazilian Health Regulatory Agency.

review and the request for a Conitec evaluation. Shorter and more homogeneous time lags were found in T3.

In a literature review by Morris *et al.* (3), the authors discussed the trend toward convergence over a 17-year time lag. The empirical studies cited in the review had different methods, with varying start and end points for measuring time. Eder *et al.* (4) analyzed 113 innovative FDA-approved drugs from 1999 to 2013 and found a median time lag of 22 years from the discovery of a therapeutic target to FDA regulatory approval. McNamee *et al.* (1) evaluated 138 new drugs approved by the FDA between 2010 and 2014 and found a time lag of 36 years, initiating the count from the growth of scientific publications on biomarkers related to the disease. Hanney *et al.* (2) focused on the investigation of time lags in the UK health system based on the analysis of two synthetic drugs: amlodipine, used in cardiovascular diseases, and olanzapine, used in mental health. The authors included markers from basic (preclinical) research.

At T3 stages, the time lags for drug inclusion in clinical guidelines and financing policies were considered. The observed time lags were 23 years for amlodipine and 20 years for olanzapine. The present study identified no similar comparable studies conducted in Brazil.

The literature shows a diversity of markers in a total of up to five translational research stages, yet there is no consensus on which and how many markers correspond to a particular stage (8). This situation may be related to the multiplicity of translational research meanings in biomedical research (37). Whenever possible, individualized data were sought from published studies to calculate the time lag with markers similar to the ones used in this study. At T1, the mean time lag from clinical trials to drug registration with the FDA was 12 years as reported by McNamee *et al.* (1). Hanney *et al.* (2) reported an approximate time lag of four years from publication of the results of the amlodipine phase I clinical trial to registration with the EMA. For



olanzapine, registered in 1996, the time lag was negative because the results of a phase I clinical study that started in 1986 were only cited in a study published in 1997. In the present study, T1 mean time was 5.30 years, which is shorter than the time identified by McNamee *et al.* (1) but longer than the amlodipine time lag reported by Hanney *et al.* (2). As for T2 time lag, the inclusion of amlodipine in the UK clinical guidelines took approximately 13 years, counted from the initial health registration. For olanzapine, this lag was 6 years. Thus, for amlodipine, the sum of T1 and T2 corresponds to 17 years. In the present study, the sum of T1 and T2 was 10.4 years, shorter than the one calculated for amlodipine. The limited comparison with the studies is highlighted, especially due to (I) inaccurate starting points for the clinical trial markers; and (II) unique health system contexts and different types of drugs (synthetic versus biological).

Abatacept, certolizumab, golimumab, and tocilizumab had negative time lags between the publication of the systematic reviews and the product registration by Anvisa. This may be partly due to the Anvisa registration having occurred, for the most part, after FDA and EMA registrations. With the exception of tocilizumab, systematic reviews were published after the date of registration in those agencies. Brazil has a large consumer market, with a diverse pharmacological-epidemiological profile, an internationally compatible ethical and sanitary environment, and professional capacities and infrastructure with potential for the internationalization of clinical research (38,39). Nevertheless, a first FDA or EMA registration may reflect several factors, including: (I) the greater innovative technological density and concentration of pharmaceutical companies based in the United States and Europe; (II) skills in conducting clinical trials, especially those with greater complexity and innovation, such as phase I and II; and (III) greater investments by the United States and European countries in research, development, and innovation (40,41).

According to McNamee *et al.* (1), basic research advances may positively reflect on the characterization of molecular targets for drugs and on clinical trial designs. In the context of rheumatoid arthritis in the 1990s, the literature already indicated that pro-inflammatory cytokines, especially tumor necrosis factor (TNF), played an important role in its pathogenesis (42,43). The development of many biological DMARDs was based on this knowledge, particularly golimumab, an anti-TNF agent. This drug had the shortest time lag in the three stages of the translational research, with 8.57 years. Its clinical development has very close

dates between clinical trial records and result publications. For example, phase II started in November 2003 and the primary outcome was concluded in February 2005 (44). In a few months, one of the phase III studies was commenced in December 2005 and completed its primary outcome in September 2007 (45). Publications with phase I, II, and III results occurred in March 2007, February 2008, and December 2008, respectively (46-48).

Undesirable delays occur when more time than necessary is spent to develop activities according to ethical, sanitary, and best practice standards. T1 activities classically take about 10 to 20 years during drug development (4,49), with low probability of success (50,51) and million to billion dollar costs (49,52,53). A significant part of this time is invested in clinical trials and includes processes such as ethical and health authorizations, registration of the clinical trial on registration platforms (e.g., ClinicalTrials.gov), and submission of the clinical development dossier to the health authority for registration purposes. Implementation strategies could still be applied in the development of clinical research to accelerate the translation of knowledge into its use in real world scenarios (54). In Brazil, evaluation processes for the registration of drugs by Anvisa have been increasingly transparent and delimited. The setting of maximum deadlines for the final decision in registration and post-registration change processes stands out, with 120 days for priority drugs and 365 for others (55,56).

T2 delays occur in the dissemination and scientific publication of clinical trial results, as well as in the generation of evidence that supports health technology assessment (HTA) processes. The publication of clinical trial results is considered an ethical and scientific conduct obligation (57). The World Health Organization recommends that such results be submitted to peer-reviewed journals within 12 months of study completion, with a view of being published within 24 months (58). However, studies (59,60) indicate low percentages of clinical trials that reported results within 12 months: 40.9% (1,722/4,209 trials) on the ClinicalTrials.gov platform and 49.5% (3,601/7,274 trials) on the EU Clinical Trials Register. Communicating results is important for several reasons; it avoids exposing research participants to ineffective interventions (57,58), reduces selective reporting bias (61,62), avoids funding research with ineffective technologies (63), generates data and information for HTA processes, knowledge translation, and clinical guideline constitution, and informs decision-making in clinical and management settings (57,63,64).

The shortest time lags at T2 were related to Conitec processes. This may be a reflection of the HTA institutionalization and improvement in Brazil over the years. The definition of procedures and deadlines in Law no. 12.401/2011 provides a solid guideline for structuring and implementing activities in the country (25,65). It is noteworthy that Conitec has similar structure and functioning policies compared to HTA agencies in Australia, Canada, and the United Kingdom (66). Transparency and civil society participation are also guaranteed in regulatory frameworks and have advanced in recent years, although they may differ (65,67,68).

### *Literature contributions and study limitations*

This study contributes to the literature in several aspects. First, a translational research steps model adapted to the Brazilian case was adopted (28), which allowed a closer approximation with the reality of the country. Second, explicit, transparent, and reproducible methods were adopted for each marker, increasing the reliability of the results obtained. Third, the adopted methodology can be used for other drugs to investigate whether there are associated factors that influence the course of time from drug discovery to use in clinical settings. These include factors such as type of disease (prevalent versus rare), type of drug (synthetic versus biological), the existence of generics available at the time of incorporation, the type of applicant for Conitec assessment (SUS versus non-SUS). Fourth, it provides time lag estimates for an upper-middle-income country with marked socioeconomic health inequalities. As far as we know, time lag estimates published in the literature come from high-income countries.

Some limitations of the study should be noted. First, there was a high heterogeneity in the definition of markers for each stage of translational research in published studies, which limits the comparison of time lags between studies. To get around this limitation, we tried to calculate the time lag between the markers used in this study when this information was available. Second, our empirical strategy was restricted to the five biological DMARDs for rheumatoid arthritis. Thus, the lags estimated in this study may not be extrapolated to other classes of drugs, diseases, drugs demanding incorporation into the SUS, and the form of drug acquisition. Therefore, it is important to study other drugs. In addition, the average time it takes to switch from one biological to another is also not included in the time interval estimated in this study. When few treatment

alternatives are available, patients may experience a longer delay when they need to access other DMARDs. Third, our estimates may contain some inaccuracies as some data sources only show the month and year of the marker. In this case, we adopted the rule of considering day 15 of each month. Fourth, there may be other scientific articles or information disclosures with clinical trial results that were not identified through our sensitive search strategy. This could influence the measured time lag.

### *Implications and perspectives for health policy, clinical practice, and research*

Some implications for health policy and clinical practice lie in the fact that the results presented here can be used to find out whether the time lag is compatible with the desired situation. Policy makers, the production sector, researchers, and society must ask themselves what the optimal deadlines are to access the technologies available, guaranteeing safety, efficiency, quality, and rationality. Specifically in the clinical practice, the benefits of faster translation of new biological drugs can expand therapeutic options for managing the disease on time. With this, patients could have better results and quality of life, such as control of erosive joint damage and fewer extra-articular complications. Thus, the reasonable time frame to make the drug available would require the completion of each of the stages of the translational research. By establishing plausible deadlines for carrying out the steps, factors that impact, positively or negatively, on reaching the agreed deadline and the consequent implementation of access programs and rational use of medicines could be investigated. Above all, there is the opportunity to improve legal frameworks to guarantee timely access to technologies. The creation of a schedule for the translation of knowledge, implementation, and use of evidence in the context of translational research would be an area of special interest to promote more healthcare benefits to society in a shorter period. Nevertheless, improving the sharing of documents and experiences among regulatory agencies could accelerate the analysis needed for registration and HTA in health systems.

Among the implications for further research, we specifically highlight two: the need for a standardization of translational research markers and research involving more drug categories. Based on the results of this research, studies could be carried out with application of the method to a larger sample with other types of drugs and analyses of factors related to an increased or reduced time lag.

## Conclusions

The objective of this study was to estimate the time lag of translational research of biological drugs incorporated into the Brazilian Unified Health System between 2012 and 2019 for the treatment of rheumatoid arthritis. The mean time lag from the publication of the results of phase I clinical trials to the first SUS dispensing was 11.13 years. A shorter period was observed in the Brazilian case when it was possible to compare markers between studies. Brazil has instituted legal frameworks that set deadlines for sanitary registration and the assessment of health technologies and their availability in the SUS, which allows reducing stage 2 translational research lags. Improvements are still needed in the T1 and T2 stages, especially in conducting clinical trials and publishing their results. Future research should investigate associated factors that influence the course of time.

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## Footnote

*Peer Review File:* Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-397/prf>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-397/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Approval by an ethics committee is not applicable as this research used secondary data available in the public domain.

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Supplementary Appendix

**How long does it take to translate research findings into routine healthcare practice? The case of biological drugs for rheumatoid arthritis in Brazil**

Evandro de Oliveira Lupatini, Ivan Ricardo Zimmermann, Jorge Otávio Maia Barreto, Everton Nunes da Silva

**Appendix 1** Search strategies ..... 2  
**Appendix 2** Marker event dates of the five biological DMARDs ..... 7

**Appendix 1** Search strategies - Abatacept for rheumatoid arthritis

| Marker event  | Data source        | Search strategy  | Result | Search date |
|---|--------------------|--|--------|-------------|
| Publication of phase I, II and III clinical trial results | MEDLINE (PubMed)   | ("Abatacept"[Mesh] OR "Abatacept"[TIAB] OR "LEA29Y"[TIAB] OR " BMS224818"[TIAB] OR " BMS-224818"[TIAB] OR "BMS 224818"[TIAB] OR "Belatacept"[TIAB] OR "Orencia"[TIAB] OR "BMS 188667"[TIAB] OR "BMS-188667"[TIAB] OR "BMS188667"[TIAB] OR "CTLA-4-Ig"[TIAB] OR "CTLA4-Ig"[TIAB] OR "CTLA4-Fc"[TIAB] OR "Nulojix"[TIAB]) AND ("Arthritis, Rheumatoid"[Mesh] OR "Rheumatoid"[TIAB] OR "Arthritis"[TIAB]) AND Therapy/Broad[filter] | 969    | 05/10/2019  |
| Publication of systematic review                          | MEDLINE (PubMed)   | ("Abatacept"[Mesh] OR "Abatacept"[TIAB] OR "LEA29Y"[TIAB] OR " BMS224818"[TIAB] OR " BMS-224818"[TIAB] OR "BMS 224818"[TIAB] OR "Belatacept"[TIAB] OR "Orencia"[TIAB] OR "BMS 188667"[TIAB] OR "BMS-188667"[TIAB] OR "BMS188667"[TIAB] OR "CTLA-4-Ig"[TIAB] OR "CTLA4-Ig"[TIAB] OR "CTLA4-Fc"[TIAB] OR "Nulojix"[TIAB]) AND ("Arthritis, Rheumatoid"[Mesh] OR "Rheumatoid"[TIAB] OR "Arthritis"[TIAB]) AND systematic[sb]        | 83     | 05/10/2019  |
| Phase I, II and III clinical trial registries             | ClinicalTrials.gov | Abatacept OR LEA29Y OR BMS224818 OR BMS-224818 OR BMS 224818 OR Belatacept OR Orencia OR BMS 188667 OR BMS-188667 OR BMS188667 OR CTLA-4-Ig OR CTLA4-Ig OR CTLA4-Fc OR Nulojix   Arthritis   | 131    | 05/10/2019  |

Results – Abatacept for rheumatoid arthritis

| Marker event                                    | Date       | Reference   |
|---|------------|---|
| Publication of phase I clinical trial results   | Not found  | Not found   |
| Publication of phase II clinical trial results  | 06/06/2002 | Moreland <i>et al.</i> Costimulatory blockade in patients with rheumatoid arthritis: a pilot, dose-finding, double-blind, placebo-controlled clinical trial evaluating CTLA-4Ig and LEA29Y eighty-five days after the first infusion. <i>Arthritis Rheum</i> 2002;46:1470-1479 DOI: 10.1002/art.10294 |
| Publication of phase III clinical trial results | 11/13/2003 | Kremer <i>et al.</i> Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. <i>N Engl J Med.</i> 2003 Nov 13;349(20):1907-15. DOI: 10.1056/NEJMoa035075  |
| Publication of systematic review                | 11/01/2006 | Nogid A1, Pham DQ. Role of abatacept in the management of rheumatoid arthritis. <i>Clin Ther.</i> 2006 Nov;28(11):1764-78. DOI: 10.1016/j.clinthera.2006.11.020   |



Search strategies – Certolizumab for rheumatoid arthritis

| Marker event  | Data source        | Search strategy  | Result | Search date |
|---|--------------------|--|--------|-------------|
| Publication of phase I, II and III clinical trial results | MEDLINE (PubMed)   | ((("Certolizumab Pegol"[MeSH Terms] OR "Cimzia"[Title/Abstract]) OR "CDP870"[Title/Abstract]) OR "CDP 870"[Title/Abstract]) AND (((("arthritis, rheumatoid"[MeSH Terms] OR "Rheumatoid Arthritis"[Title/Abstract]) OR "Arthritis"[MeSH Terms]) OR "Arthritis"[Title/Abstract])   | 685    | 05/14/2020  |
| Publication of systematic review                          | MEDLINE (PubMed)   | (((((certolizumab pegol[MeSH Terms]) OR ("Certolizumab"[Title/Abstract])) OR ("Certolizumab pegol"[Title/Abstract])) OR ("Cimzia"[Title/Abstract]) OR ("CDP870"[Title/Abstract]) OR ("CDP 870"[Title/Abstract])) AND (((("arthritis, rheumatoid"[MeSH Terms] OR "Rheumatoid Arthritis"[Title/Abstract]) OR "Arthritis"[MeSH Terms]) OR "Arthritis"[Title/Abstract])) AND (((("Systematic Review"[Title/Abstract] OR "Review"[Publication Type]) OR "Systematic Reviews as Topic"[MeSH Terms]) OR "Systematic Review"[Publication Type])) | 271    | 05/14/2020  |
| Phase I, II and III clinical trial registries             | ClinicalTrials.gov | certolizumab   Arthritis, Rheumatoid   | 85     | 05/14/2020  |

Results – Certolizumab for rheumatoid arthritis

| Marker event                                    | Date       | Reference   |
|---|------------|---|
| Publication of phase I clinical trial results   | Not found  | Not found   |
| Publication of phase II clinical trial results  | 10/01/2002 | Choy EH, Hazleman B, Smith M, <i>et al.</i> Efficacy of a novel PEGylated humanized anti-TNF fragment (CDP870) in patients with rheumatoid arthritis: a phase II double-blinded, randomized, dose-escalating trial. <i>Rheumatology (Oxford)</i> . 2002;41(10):1133-1137. doi:10.1093/rheumatology/41.10.1133   |
| Publication of phase III clinical trial results | 10/30/2008 | Keystone E, Heijde Dv, Mason D Jr, <i>et al.</i> Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study [published correction appears in <i>Arthritis Rheum</i> . 2009 May;60(5):1249]. <i>Arthritis Rheum</i> . 2008;58(11):3319-3329. doi:10.1002/art.23964 |
| Publication of systematic review                | 05/06/2010 | Nam JL, Winthrop KL, van Vollenhoven RF, <i>et al.</i> Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA [published correction appears in <i>Ann Rheum Dis</i> . 2011 Aug;70(8):1519]. <i>Ann Rheum Dis</i> . 2010;69(6):976-986. doi:10.1136/ard.2009.126573  |

Search strategies – Golimumab for rheumatoid arthritis

| Marker event  | Data source        | Search strategy   | Result | Search date |
|---|--------------------|---|--------|-------------|
| Publication of phase I, II and III clinical trial results | MEDLINE (PubMed)   | ((("golimumab"[Supplementary Concept] OR "golimumab"[Title/Abstract]) OR "Simponi"[Title/Abstract] OR "cnto 148"[Title/Abstract] OR "cnto 148"[Title/Abstract]) AND (((("arthritis, rheumatoid"[MeSH Terms] OR "Rheumatoid Arthritis"[Title/Abstract] OR "Arthritis"[MeSH Terms]) OR "Arthritis"[Title/Abstract]))  | 779    | 05/06/2020  |
| Publication of systematic review                          | MEDLINE (PubMed)   | (((((("golimumab"[Supplementary Concept] OR "golimumab"[Title/Abstract]) OR "Simponi"[Title/Abstract] OR "cnto 148"[Title/Abstract] OR "cnto 148"[Title/Abstract])) AND (((("arthritis, rheumatoid"[MeSH Terms] OR "Rheumatoid Arthritis"[Title/Abstract] OR "Arthritis"[MeSH Terms]) OR "Arthritis"[Title/Abstract]))) AND (((("Systematic Review"[Title/Abstract] OR "Review"[Publication Type]) OR "Systematic Reviews as Topic"[MeSH Terms]) OR "Systematic Review"[Publication Type])) | 272    | 05/06/2020  |
| Phase I, II and III clinical trial registries gov         | ClinicalTrials.gov | golimumab   Arthritis, Rheumatoid   | 51     | 05/06/2020  |

Results – Golimumab for rheumatoid arthritis

| Marker event                                    | Date       | Reference  |
|---|------------|--|
| Publication of phase I clinical trial results   | 03/01/2007 | Zhou H, Jang H, Fleischmann RM, <i>et al.</i> Pharmacokinetics and safety of golimumab, a fully human anti-TNF-alpha monoclonal antibody, in subjects with rheumatoid arthritis. <i>J Clin Pharmacol.</i> 2007;47(3):383-396. doi:10.1177/0091270006298188   |
| Publication of phase II clinical trial results  | 03/27/2008 | Kay J, Matteson EL, Dasgupta B, <i>et al.</i> Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study [published correction appears in <i>Arthritis Rheum.</i> 2010 Nov;62(11):3518]. <i>Arthritis Rheum.</i> 2008;58(4):964-975. doi:10.1002/art.23383                                   |
| Publication of phase III clinical trial results | 12/09/2008 | Keystone EC, Genovese MC, Klareskog L, <i>et al.</i> Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study [published correction appears in <i>Ann Rheum Dis.</i> 2011 Jan;70(1):238]. <i>Ann Rheum Dis.</i> 2009;68(6):789-796. doi:10.1136/ard.2008.099010 |
| Publication of systematic review                | 01/20/2010 | Singh JA, Noorbaloochi S, Singh G. Golimumab for rheumatoid arthritis. <i>Cochrane Database Syst Rev.</i> 2010;(1):CD008341. Published 2010 Jan 20. doi:10.1002/14651858.CD008341  |

Search strategies – Rituximab for rheumatoid arthritis

| Marker event  | Data source        | Search strategy  | Result | Search date |
|---|--------------------|--|--------|-------------|
| Publication of phase I, II and III clinical trial results | MEDLINE (PubMed)   | ((((((((((("Rituximab"[MeSH Terms] OR "cd20 antibody rituximab"[Title/Abstract]) ) OR "Mabthera"[Title/Abstract]) OR "idec c2b8 antibody"[Title/Abstract]) OR "idec c2b8"[All Fields]) OR "idec c2b8"[Title/Abstract]) OR "idec c2b8"[Title/Abstract]) OR "GP2013"[Title/Abstract]) OR "Rituxan"[Title/Abstract]) OR "Rituximab"[Title/Abstract]) AND (((("arthritis, rheumatoid"[MeSH Terms] OR "Rheumatoid Arthritis"[Title/Abstract]) OR "Arthritis"[MeSH Terms]) OR "Arthritis"[Title/Abstract]))  | 2120   | 05/10/2020  |
| Publication of systematic review                          | MEDLINE (PubMed)   | ((((((((((("Rituximab"[MeSH Terms] OR "rituximab"[Title/Abstract] OR "cd20 antibody rituximab"[Title/Abstract]) ) OR "Mabthera"[Title/Abstract]) OR "idec c2b8 antibody"[Title/Abstract]) OR "idec c2b8 antibody"[Title/Abstract]) OR "idec c2b8"[All Fields]) OR "idec c2b8"[Title/Abstract]) OR "idec c2b8"[Title/Abstract]) OR "GP2013"[Title/Abstract]) OR "Rituxan"[Title/Abstract])) AND (((("arthritis, rheumatoid"[MeSH Terms] OR "Rheumatoid Arthritis"[Title/Abstract]) OR "Arthritis"[MeSH Terms]) OR "Arthritis"[Title/Abstract])) AND (((("Systematic Review"[Title/Abstract] OR "Review"[Publication Type]) OR "Systematic Reviews as Topic"[MeSH Terms]) OR "Systematic Review"[Publication Type])) | 738    | 05/10/2020  |
| Phase I, II and III clinical trial registries             | ClinicalTrials.gov | rituximab   Arthritis, Rheumatoid  | 114    | 05/10/2020  |

Results – Rituximab for rheumatoid arthritis

| Marker event                                    | Date       | Reference  |
|---|------------|--|
| Publication of phase I clinical trial results   | 06/17/2004 | Edwards JC, Szczepanski L, Szechinski J, <i>et al.</i> Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. <i>N Engl J Med.</i> 2004;350(25):2572-2581. doi:10.1056/NEJMoa032534   |
| Publication of phase II clinical trial results  | 04/28/2006 | The Efficacy and Safety of Rituximab in Patients With Active Rheumatoid Arthritis Despite Methotrexate Treatment: Results of a Phase IIb Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Trial  |
| Publication of phase III clinical trial results | 08/31/2006 | Cohen SB, Emery P, Greenwald MW, <i>et al.</i> Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. <i>Arthritis Rheum.</i> 2006;54(9):2793-2806. doi:10.1002/art.22025 |
| Publication of systematic review                | 10/07/2009 | Biologics for rheumatoid arthritis: an overview of Cochrane reviews (Review)   |

Search strategies – Tocilizumab for rheumatoid arthritis

| Marker event  | Data source        | Search strategy   | Result | Search date |
|---|--------------------|---|--------|-------------|
| Publication of phase I, II and III clinical trial results | MEDLINE (PubMed)   | ((((((((((((tocilizumab[Supplementary Concept]) OR ("tocilizumab"[Title/Abstract])) OR ("RHPM-1"[Title/Abstract])) OR ("RG-1569"[Title/Abstract])) OR ("R-1569"[Title/Abstract])) OR ("MSB11456"[Title/Abstract])) OR ("MSB-11456"[Title/Abstract])) OR ("atlizumab"[Title/Abstract])) OR ("MRA"[Title/Abstract])) OR ("RO-4877533"[Title/Abstract])) OR ("Actemra"[Title/Abstract])) OR ("roactemra"[Title/Abstract])) OR ("roactemra"[Title/Abstract])) AND (((("arthritis, rheumatoid"[MeSH Terms] OR "Rheumatoid Arthritis"[Title/Abstract] OR "Arthritis"[MeSH Terms] OR "Arthritis"[Title/Abstract]))   | 1921   | 05/09/2020  |
| Publication of systematic review(PubMed)                  | MEDLINE (PubMed)   | ((((((((((((((((tocilizumab[Supplementary Concept]) OR ("tocilizumab"[Title/Abstract])) OR ("RHPM-1"[Title/Abstract])) OR ("RG-1569"[Title/Abstract])) OR ("R-1569"[Title/Abstract])) OR ("MSB11456"[Title/Abstract])) OR ("MSB-11456"[Title/Abstract])) OR ("atlizumab"[Title/Abstract])) OR ("MRA"[Title/Abstract])) OR ("RO-4877533"[Title/Abstract])) OR ("Actemra"[Title/Abstract])) OR ("roactemra"[Title/Abstract])) OR ("roactemra"[Title/Abstract])) AND (((("arthritis, rheumatoid"[MeSH Terms] OR "Rheumatoid Arthritis"[Title/Abstract] OR "Arthritis"[MeSH Terms] OR "Arthritis"[Title/Abstract])) AND (((("Systematic Review"[Title/Abstract] OR "Review"[Publication Type] OR "Systematic Reviews as Topic"[MeSH Terms] OR "Systematic Review"[Publication Type])) | 526    | 05/09/2020  |
| Phase I, II and III clinical trial registries             | ClinicalTrials.gov | "Arthritis, Rheumatoid"   "tocilizumab" OR "roactemra"  | 218    | 05/09/2020  |

Results – Tocilizumab for rheumatoid arthritis

| Marker event                                    | Date       | Reference   |
|---|------------|---|
| Publication of phase I clinical trial results   | 12/12/2002 | Choy EH, Isenberg DA, Garrood T, <i>et al.</i> Therapeutic benefit of blocking interleukin-6 activity with an anti-interleukin-6 receptor monoclonal antibody in rheumatoid arthritis: a randomized, double-blind, placebo-controlled, dose-escalation trial. <i>Arthritis Rheum.</i> 2002;46(12):3143-3150. doi:10.1002/art.10623                    |
| Publication of phase II clinical trial results  | 12/12/2002 | Choy EH, Isenberg DA, Garrood T, <i>et al.</i> Therapeutic benefit of blocking interleukin-6 activity with an anti-interleukin-6 receptor monoclonal antibody in rheumatoid arthritis: a randomized, double-blind, placebo-controlled, dose-escalation trial. <i>Arthritis Rheum.</i> 2002;46(12):3143-3150. doi:10.1002/art.10623                    |
| Publication of phase III clinical trial results | 05/03/2007 | Nishimoto N, Hashimoto J, Miyasaka N, <i>et al.</i> Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab. <i>Ann Rheum Dis.</i> 2007;66(9):1162-1167. doi:10.1136/ard.2006.068064 |
| Publication of systematic review                | 10/28/2008 | Plushner SL. Tocilizumab: an interleukin-6 receptor inhibitor for the treatment of rheumatoid arthritis. <i>Ann Pharmacother.</i> 2008;42(11):1660-1668. doi:10.1345/aph.1L268  |

**Appendix 2** Marker event dates of the five biological DMARDs

| Step | Marker   | Drugs      |              |           |           |             |
|------|--|------------|--------------|-----------|-----------|-------------|
|      |  | abatacept  | certolizumab | golimumab | rituximab | tocilizumab |
| T1   | Publication of the results of the first phase I clinical trial   | N/F        | N/F          | 3/1/2007  | 6/17/2004 | 12/12/2002  |
|      | Publication of the results of the first phase II clinical trial  | 6/6/2002   | 10/1/2002    | 3/27/2008 | 4/28/2006 | 12/12/2002  |
|      | Publication of the results of the first phase III clinical trial | 11/13/2003 | 10/30/2008   | 12/9/2008 | 8/31/2006 | 5/3/2007    |
|      | Approval of the first health registration by Anvisa              | 6/25/2007  | 5/23/2011    | 4/11/2011 | 7/3/2006  | 1/19/2009   |
|      | Approval of the first health registration by FDA                 | 12/23/2005 | 5/13/2009    | 4/24/2009 | 2/28/2006 | 1/8/2010    |
|      | Approval of the first health registration by EMA                 | 5/21/2007  | 10/1/2009    | 10/1/2009 | 9/29/2006 | 1/15/2009   |
| T2   | Publication of the first review with systematic search           | 11/1/2006  | 5/6/2010     | 1/20/2010 | 10/7/2009 | 10/28/2008  |
|      | Assessment request from Conitec                                  | 3/14/2012  | 1/26/2012    | 6/21/2012 | 5/16/2012 | 5/16/2012   |
|      | Conitec initial recommendation                                   | 6/1/2012   | 6/1/2012     | 6/1/2012  | 6/1/2012  | 6/1/2012    |
|      | Conitec final decision   | 7/5/2012   | 7/5/2012     | 7/5/2012  | 7/5/2012  | 7/5/2012    |
|      | Ministry of Health decision                                      | 9/11/2012  | 9/11/2012    | 9/11/2012 | 9/11/2012 | 9/11/2012   |
|      | Guideline, manual, guide, or protocol publication                | 6/28/2013  | 6/28/2013    | 6/28/2013 | 6/28/2013 | 6/28/2013   |
| T3   | Registration of the first purchase after incorporation           | 1/30/2013  | 1/29/2013    | 4/24/2013 | 3/7/2013  | 5/17/2013   |
|      | First dispensing record  | 4/15/2013  | 8/15/2013    | 7/15/2013 | 4/15/2013 | 6/15/2013   |

N/F: not found.