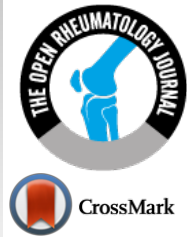




# The Open Rheumatology Journal

Content list available at: <https://openrheumatologyjournal.com>



## RESEARCH ARTICLE

### Storage Conditions of Immunobiologicals and their Influence on the Efficacy and Safety in the Treatment of Autoimmune Rheumatic Diseases

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#### Abstract:

#### Objective:

The study aimed to evaluate the influence of storage temperature on immunobiological efficacy and safety in autoimmune rheumatic disease treatment.

#### Methods:

This observational study included adult patients with autoimmune rheumatic diseases who used immunobiologicals stored at home and were followed up at the rheumatology outpatient clinic of the General University Hospital of Cuiabá, Mato Grosso, Brazil, in 2017/2018. Patients were evaluated regarding disease activity and occurrence of adverse events, and a household survey of the temperature of the storage environment of these drugs was conducted.

#### Results:

Sixty patients with a mean age of 50.4 years were evaluated. Of these, 39 patients (65%) stored their biological drugs outside the recommended temperature range. Storage of the immunobiological at the incorrect temperature was 76% higher among patients with moderate/high rheumatic disease activity ( $p=0.003$ ).

#### Conclusion:

Most patients stored their immunobiologicals outside the temperature range recommended in the package insert, and there was an association between incorrect storage temperature and moderate/high autoimmune rheumatic disease activity.

**Keywords:** Biological therapy, Ambient temperature, Rheumatic diseases, Antirheumatic agents, Immunobiologicals, Biological drugs.

#### Article History

Received: January 12, 2020

Revised: April 21, 2020

Accepted: May 03, 2020

## 1. INTRODUCTION

Treatment of autoimmune rheumatic diseases involves the use of immunobiologicals, which are thermolabile and parenteral, requiring careful storage at recommended temperatures to maintain their efficacy and safety [1 - 8].

Biological drugs are formed by highly complex protein molecules, and their structural integrity must be preserved to avoid interfering with their biological activity [9 - 11]. Both chemical and physical instability can contribute to a loss of activity through the formation of protein aggregates, which

leads to increased immunogenicity and the formation of anti-drug antibodies, which may cause reduced efficacy and a risk of adverse reactions [12 - 18].

Controlled storage, distribution and transport of temperature-sensitive products are essential factors to ensure quality [19 - 22]. Biological disease-modifying antirheumatic drugs (bDMARDs) should be stored at 2 to 8 degrees Celsius according to the manufacturers' instructions [3 - 8]. The transport of biological products should be monitored continuously, from the manufacturer to the wholesaler to the pharmacy, with regard to temperature maintenance to ensure the quality of the product until its distribution [19]. In Brazil, bDMARDs are accessed *via* state health secretariats through the Specialized Pharmaceutical Care Program, which dispenses

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them directly to patients, who are then responsible for their storage and administration. Observational studies have shown that the home storage temperatures of bDMARDs frequently deviate from the recommended temperature range [23 - 25]. Therefore, this study evaluates the effect of storage temperature on immunobiological drug efficacy and safety in the treatment of patients with autoimmune rheumatic diseases.

## 2. METHODS

### 2.1. Study Design and Population

We conducted a descriptive cross-sectional epidemiological study that evaluated and surveyed patients seen at the rheumatology outpatient clinic of the General University Hospital of Cuiabá, Mato Grosso (MT), Brazil, in 2017/2018.

Patients eligible for inclusion were adults of both sexes, living in Cuiabá or Várzea Grande (MT), diagnosed with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis, and using injectable subcutaneous bDMARDs (adalimumab, etanercept, golimumab, secukinumab, certolizumab pegol and abatacept) stored at home.

Because this was a field study involving humans, it was submitted for evaluation to the Ethics and Research Committee. Participation was voluntary and occurred after participants signed an informed consent form. The participants were given verbal and written instructions on the study objectives, data collection technique and data anonymity.

### 2.2. Procedure

We used a survey instrument in the form of a structured questionnaire to collect data from 60 patients who agreed to participate. Data on patient personal and socioeconomic characteristics, treatment, drug transport and storage conditions between the pharmacy and the home and medical evaluation with the application of disease activity indexes were collected. A home visit was subsequently scheduled to measure the storage temperature of the biological drug. No additional advice on drug storage was given as part of this study, and the patients were instructed to follow the instructions contained in the package inserts of the bDMARDs. A digital infrared thermometer with a range of -20 to 400 °C (MT-320, Minipa) was used to measure temperature.

### 2.3. Primary Outcome

The primary outcome was the proportion of patients who stored bDMARDs within the temperature range recommended in the package inserts (storage at the correct temperature) and those who did not store in this temperature range (storage at the wrong temperature). To assess the effects of home storage of

MMCD-b in the treatment of patients, in relation to the assessment of efficacy, the ICAD (composite disease activity indexes) for each specific rheumatic disease were calculated. These include clinical and laboratory components. In rheumatoid arthritis, the main ICADs are the disease activity index Disease Activity Score 28 (DAS 28), the Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI). There is a good correlation between these ICAD, making it possible to use any of them in isolation [26]. In this study, three indices were used to assess disease activity in rheumatoid arthritis: DAS 28, SDAI / CDAI. In psoriatic arthritis, the use of the following indices is recommended: Disease Activity in Psoriatic Arthritis (DAPSA) for the assessment of peripheral arthritis ; Ankylosing Spondylitis Disease Activity Score (ASDAS), for the assessment of axial arthritis [27 - 29]. For the skin component, the tool Psoriasis Area Severity Index (PASI) is recommended [30]. To assess disease activity in psoriatic arthritis, the following indices were applied: DPSA, PASI and ASDAS. The assessment of disease activity in ankylosing spondylitis can be done using the BASDAI score and ASDAS [28 - 31]. In this research, these two indices were measured.

The patients were classified into two groups according to the result of ICAD in remission / low activity or moderate / high disease activity and we correlated the assessment of disease activity with the storage temperature of MMCD-b (correct or incorrect). All patients were questioned about the occurrence of adverse reactions with the use of bDMARDs. The following post-application reactions of the immunobiological drug were reported: erythema, itching, edema on the spot, euphoria, cellulitis and hypotension and one case of herpes zoster.

### 2.4. Data Analysis

Categorical variables are summarized using absolute and relative frequencies. The Pearson chi-square or Fisher exact tests were used to assess the existence of significant associations between categorical variables, and the Prevalence Ratio (PR) was used as a measure of the strength of this association in a bivariate analysis of the variables. The interaction between the variables was analysed by Poisson regression with robust variance. All analyses were performed using Stata Statistical Software® 13.0 (College Station, Texas, USA), and a p-value  $\leq 0.05$  in two-tailed tests was considered significant.

## 3. RESULTS

A total of 60 patients were evaluated, with a mean age of 50.4 years (19 (min) – 84 (max) years). The profile of this population is provided in Table 1.

**Table 1. Socioeconomic and epidemiological profile of patients with rheumatic diseases.**

| Variable   | n  | %    |
|------------|----|------|
| <b>Sex</b> | -  | -    |
| Male       | 24 | 40.0 |
| Female     | 36 | 60.0 |
| <b>Age</b> | -  | -    |
| < 60 years | 33 | 55.0 |

(Table 1) contd....

| Variable   | n  | %    |
|--|----|------|
| ≥ 60 years   | 27 | 45.0 |
| <b>Education level</b>   | -  | -    |
| Illiterate   | 5  | 8.3  |
| Primary  | 14 | 23.3 |
| Secondary  | 17 | 28.3 |
| Higher   | 24 | 40.1 |
| <b>Employed</b>  | -  | -    |
| Yes  | 41 | 68.3 |
| No   | 19 | 31.7 |
| <b>Individual monthly income</b>   | -  | -    |
| None   | 16 | 26.7 |
| 1 to 3 times the minimum wage  | 28 | 46.7 |
| 4 or more times the minimum wage   | 15 | 25.0 |
| Not provided   | 1  | 1.6  |
| <b>Monthly family income</b>   | -  | -    |
| 1 to 3 times the minimum wage  | 36 | 60.0 |
| 4 or more times the minimum wage   | 22 | 36.7 |
| Not provided   | 2  | 3.3  |
| <b>Rheumatic disease</b>   | -  | -    |
| Rheumatoid arthritis   | 36 | 60.0 |
| Ankylosing spondylitis   | 16 | 26.7 |
| Psoriatic arthritis  | 8  | 13.3 |
| <b>Immunobiological</b>  | -  | -    |
| Adalimumab   | 32 | 53.3 |
| Etanercept   | 16 | 26.7 |
| Golimumab  | 4  | 6.7  |
| Certolizumab pegol   | 2  | 3.3  |
| Abatacept  | 3  | 5.0  |
| Secukinumab  | 3  | 5.0  |
| <b>Location in the refrigerator where the immunobiological medicine was stored</b> | -  | -    |
| Shelf  | 51 | 85.0 |
| Freezer  | 1  | 1.7  |
| Drawer   | 5  | 8.3  |
| Door   | 3  | 5.0  |

All patients stored biological medicines in the refrigerator, mostly on the refrigerator shelf at home (Table 1). Considering that the correct storage temperature is 2 to 8 °C, the majority of patients stored bDMARDs at an incorrect temperature (Table 2). The mean bDMARD storage temperature was 9.9°C (95% CI, 9.0-10.9; min 3.8°C - max 20.9°C). The mean temperature of the external environment was 29.9°C (95% CI, 28.9-30.9; min 20.6 °C - max 37.9 °C).

**Table 2. bDMARD home storage temperature.**

| Variable                                      | n  | %    |
|---|----|------|
| <b>Temperature of the bDMARD storage site</b> | -  | -    |
| Correct (2 to 8 °C)                           | 21 | 35.0 |
| Incorrect (<2 or >8 °C)                       | 39 | 65.0 |

In the bivariate analysis evaluating the association between explanatory variables and incorrect temperature storage, the

occurrence of the latter was 76% higher among patients with moderate/high rheumatic disease activity. We observed 30% lower incidences of incorrect temperature storage among patients with secondary education and 50% lower incidences among patients with higher education. No significant differences were found regarding the association of adverse reactions and bDMARD storage at correct or incorrect temperatures (Table 3).

In patients with no education or primary education and with moderate/high rheumatic disease activity, the storage at incorrect temperatures was 90% higher. Among those with secondary or higher education and moderate/high rheumatic disease activity, the storage at incorrect temperatures was 92% higher. Moderate/high rheumatic disease activity was associated with incorrect storage temperatures, regardless of the education level (Table 4).

**Table 3. Patient-related factors associated with incorrect immunobiological drug storage temperature.**

| Variable                          | n (%)     | Storage Temperature |           | PR-crude (95% CI) | p-value      |
|-----------------------------------|-----------|---------------------|-----------|-------------------|--------------|
|                                   |           | Incorrect           | Correct   |                   |              |
| <b>Education level</b>            | -         | -                   | -         | -                 | -            |
| Illiterate                        | 5 (8.3)   | 5 (100.0)           | 0         | 1.00              | -            |
| Primary                           | 14 (23.3) | 10 (71.4)           | 4 (28.6)  | 0.71 (0.51-0.99)  | 0.048        |
| Secondary                         | 17 (28.3) | 12 (70.6)           | 5 (29.4)  | 0.70 (0.51-0.96)  | <b>0.027</b> |
| Higher                            | 24 (40.1) | 12 (50.0)           | 12 (50.0) | 0.50 (0.33-0.74)  | <b>0.001</b> |
| <b>Age range</b>                  | -         | -                   | -         | -                 | -            |
| 17 to 40 years                    | 12 (20.0) | 8 (66.7)            | 4 (33.3)  | 1.05 (0.64-1.74)  | 0.82         |
| 41 to 59 years                    | 21 (35.0) | 14 (66.7)           | 7 (33.3)  | 1.05 (0.69-1.61)  | 0.79         |
| 60 to 84 years                    | 27 (45.0) | 17 (63.0)           | 10 (37.0) | 1.00              | -            |
| <b>Employed</b>                   | -         | -                   | -         | -                 | -            |
| Yes                               | 41 (68.3) | 24 (58.5)           | 17 (41.5) | 0.74 (0.52-1.04)  | 0.12         |
| No                                | 19 (31.7) | 15 (78.9)           | 4 (21.1)  | 1.00              | -            |
| <b>Monthly income</b>             | -         | -                   | -         | -                 | -            |
| None                              | 16 (27.1) | 12 (75.0)           | 4 (25.0)  | 1.00              | -            |
| 1 to 3 xMW                        | 28 (47.5) | 18 (64.3)           | 10 (35.7) | 0.85 (0.57-1.27)  | 0.45         |
| 4 or more xMW                     | 15 (25.4) | 9 (60.0)            | 6 (40.0)  | 0.80 (0.48-1.32)  | 0.38         |
| <b>Adverse reaction</b>           | -         | -                   | -         | -                 | -            |
| Yes                               | 12 (20.0) | 7 (58.3)            | 5 (41.7)  | 0.87 (0.52-1.46)  | 0.58         |
| No                                | 48 (80.0) | 32 (66.7)           | 16 (33.3) | 1.00              | -            |
| <b>Rheumatic disease activity</b> | -         | -                   | -         | -                 | -            |
| Remission/low                     | 33 (55.0) | 16 (48.5)           | 17 (51.5) | 1.00              | -            |
| Moderate/high                     | 27 (45.0) | 23 (85.2)           | 4 (14.8)  | 1.76 (1.19-2.58)  | <b>0.003</b> |

Legend: xMW=times the minimum wage.

**Table 4. Interaction between educational level and rheumatic disease activity with incorrect immunobiological drug storage temperatures.**

| Variables   | PR   | 95% CI    | p-value      |
|---|------|-----------|--------------|
| <b>Educational level/Rheumatic disease activity</b> | -    | -         | -            |
| secondary/higher and moderate/high                  | 1.92 | 1.20-3.10 | <b>0.007</b> |
| illiterate/primary and remission/low                | 1.50 | 0.73-3.05 | 0.26         |
| illiterate/primary and moderate/high                | 1.90 | 1.17-3.09 | <b>0.009</b> |

#### 4. DISCUSSION

The studied population had an average age of 50 years old, with a predominance of females. Most of them have a higher education level, engaged in paid activity with an individual income of 1 to 3 minimum wages.

It was found that most patients (65%) with autoimmune rheumatic diseases do not store their immunobiological drugs within the temperature range recommended by the manufacturer. This result is in agreement with previous studies on home storage conditions for immunobiological drugs, such as that by Vlieand *et al.* [23], and Cuellar *et al.* [24]. Notably, these studies were conducted in countries with low external environmental temperatures, different from this study, which was conducted in a hot region, where in most cases, the storage temperature of the biological drug was above the recommended temperature.

In this study, we also observed that storage at incorrect temperatures was associated with moderate/high rheumatic

disease activity, with 76% higher incidences of inadequate temperature storage by patients with moderate/high rheumatic disease activity. As a possible explanation for this loss of efficacy, studies point to the formation of protein aggregates when these thermolabile drugs are subjected to inadequate storage temperatures [12 - 14], which can lead to the formation of anti-drug antibodies, decreasing efficacy, and may also lead to an increase in adverse events, such as a severe allergic reaction or an immune response to the immunobiological drug that induces autoimmunity [15 - 18].

Regarding the safety of bDMARD treatment, there were no significant differences regarding the association of adverse reactions and storage of the bDMARDs at correct or incorrect temperatures.

The incorrect temperature storage of biological medicines at home may have occurred due to several factors. This study was carried out in a high temperature region. We recorded an average temperature of the external environment to be 29.9°C;

this can influence the storage temperature of the biological medicine in the home refrigerator.

Patients used refrigerators that do not have temperature alarm systems and older ones, affecting the ability to maintain a consistent cold temperature [20 - 22].

In addition, some patients may have difficulty understanding the instructions provided by the medical and pharmaceutical staff. In this study, the storage of bDMARDs at incorrect temperatures was 30% lower among patients with secondary education and 50% lower among patients with higher education. However, when the rheumatic disease activity is moderate/high, the association with storage under inadequate temperatures was independent of education level.

Since, in Brazil, public health is a constitutional right, in the market for biological products in the country, the Ministry of Health is responsible for 60% of all acquisitions in this sector, which increases the interest of pharmaceutical industries in the production of such inputs. Despite meeting a relatively restricted demand, corresponding to about 2% of all medicines purchased, biological medicines comprise 40% of the pharmaceutical assistance budget by the Ministry of Health [9, 10].

Immunobiological drugs are dispensed by the Specialized Component of Pharmaceutical Assistance -Ceaf - State Secretariat of Health of Mato Grosso (SES-MT), however, the responsibility for the storage and administration of biological medicines used to treat autoimmune rheumatic diseases are of patients. There is a need to implement guidance programs on the home storage of DMARD-b, as well as, to have adequate places for the storage of these biological medicines if the patient does not have a proper refrigerator in his home to be able to maintain the refrigeration chain. Finally, the organization of medical and pharmaceutical assistance programs, with the formation of a registry and follow-up of patients after the withdrawal of DMARD-b is necessary in order to verify the effectiveness of the treatment, by measuring the activity indexes of autoimmune rheumatic diseases and checking adverse events.

As limitations, the design of this study did not allow monitoring the temperature over the full storage time of a single dispensation of the drug to the home, *i.e.*, its delivery from a pharmacy to its first use by the patient. Furthermore, we cannot state the reasons that led to incorrect storage temperatures, *i.e.*, lack of instructions, refrigerator quality and time of use, and did not assess the influence of external temperature. We also did not monitor the exact time of bDMARD administration.

Thus, prospective studies are necessary to investigate the home storage temperature conditions of immunobiological drugs and their relationship with increased immunogenicity, which affects the efficacy and safety of the treatment of autoimmune rheumatic diseases.

## CONCLUSION

Most patients stored their immunobiological drugs outside the temperature range recommended in the package insert, and the incorrect storage temperature for these drugs is associated

with lower efficacy in controlling autoimmune rheumatic disease activity.

Regarding treatment safety, there was no association between adverse reactions and storage at correct or incorrect temperatures.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the ethics and research commission (CEP) of the UNIVERSITY OF CUIABÁ (UNIC), Brazil.

## HUMAN AND ANIMAL RIGHTS

No Animals were used in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

## CONSENT FOR PUBLICATION

All patients participated on a voluntary basis and gave their informed consent.

## AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available in Institutional Repository Academic and Intellectual Production Bank at [<https://repositorio.pgskroton.com//handle/123456789/24350>].

## FUNDING

This work was supported by CAPES Foundation - Ministry of Education for Scholarships with the support of the Support Program for the Training of Higher Education Institutions (PROSUP) under grant no. 31257881884.

## CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

## ACKNOWLEDGEMENTS

We thank all the patients who willingly opened the doors of their homes for a home visit. We also thank the University General Hospital for supporting the development of this study.

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