Clinical and economic "real world" analysis of the switching from Remicade (Infliximab Reference) by Remsima (Infliximab Biosimilar) in PLANSERV patients with Rheumatoid Arthritis, Ankylosing Spondylitis and Psoriatic Arthritis.

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ABSTRACT

Background: Planserv, Health Care System of the State Public Employees of Bahia, Brazil, offers coverage of biological therapy for the pathologies of Rheumatoid Arthritis, Ankylosing Spondylitis and Psoriatic Arthritis. In August 2016, 78 patients were receiving REMICADE (Infliximab). On this date, an administrative decision reduced the value of REMICADE, equaling the same value of the drug REMSIMA (Infliximab Biosimilar). This measure promoted a change in the care behavior, causing that, from September of 2016, the patients that were using the REMICADE began to use the REMSIMA. Although international studies have shown safety and efficacy in the interchangeability between these two products (Infliximab de Reference with its Biosimilar), a study was conducted with the objective of measuring the discontinuity of the therapy, after the exchange of the referred medicines. An economic assessment was also conducted to measure the economy of this decision.

Methods: We conducted a real-world transitional study, a prospective, uncontrolled cohort, with adult patients in the Planserv Medication Support Program, diagnosed with Rheumatoid Arthritis (RA), Psoriatic Arthritis (PA) and Ankylosing Spondylitis (AS), who were already using Reference Infliximab (REMICADE) and who switched to Infliximabe Biosimilar (REMSIMA) between September 2016 and September 2017.

The primary endpoint analyzed was the “treatment discontinuity index” (for any cause), and measured by intention to treat. The secondary endpoint was the "increased disease activity" rate, measured during the study period, using the standard scores (SDAI, BASDAI and CASPAR). These scores were measured at the time of product exchange and reassessed 3 times throughout the study. It was positively considered as an increase in disease activity, any measure throughout the study, higher than the initial measure, and that was above the remission limit of the disease. The reference values to compare rates of "increased disease activity" were the same scores measured over a year before starting the study when the same patients were
using the Reference Infliximab (REMICADE), with the same methodology used in the period that used Infliximab Biosimilar (REMSIMA). To evaluate the economic impact, a cost minimization analysis was performed (drug - to - drug comparison).

**Results:** After completing the study in September 2017, 5 (6.4%) patients who switched from REMICADE to REMSIMA, discontinued therapy, with 04 (5.1%) for failure of therapy, with protocol change for another biological drug and 01 (1.3%) for loss of follow-up. The reference value found for the therapy discontinuation rate measured in the one-year period in which the patients were using REMICADE was 10 (11%) patients, 8 (9%) for failure of exchange therapy to another biological and 2 (2%) for loss of follow-up. The subgroup analyzes (by type of pathology), between the periods that the patients used the REMSIMA, compared to the period that used the REMICADE were equivalent. This rate in Rheumatoid Arthritis was 8% among REMSIMA patients and 18% among REMICADE patients. In Ankylosing Spondylitis the rate was exactly the same (3%). In the group of patients with Psoriatic Arthritis, the discontinuity rate among REMSIMA patients was 13%, whereas among patients using REMICADE there were no cases of discontinuation of therapy. We consider that the low sample number in the subgroup of Psoriatic Arthritis (08 cases and 1 discontinuity among REMSIMA patients) is certainly a confounding factor.

Analysis of the secondary outcome: The rate of "increased disease activity" occurred in 42% of patients who used REMSIMA, while the same rate in the reference period (when patients were using REMICADE) was 46%. Subgroup analyzes (by type of pathology) also showed that the rates of increase in disease activity among REMSIMA patients compared to those using REMICADE were the same, with a slight advantage for REMSIMA in the subgroup of Rheumatoid Arthritis (AR: 55% for REMSIMA versus 63% for REMICADE). The economic analysis showed that the change from REMICADE to REMSIMA led to an economy of approximately R $ 1.75 million reais (US $ 0.5 million dollars), with 1,689 REMSIMA vials dispensed in the period. Average savings of approximately R $ 135 thousand reais per month. This saving was equivalent to 28% of the cost of Infliximab therapy in the period.

**Finding:** The switching of REMICADE by REMSIMA in patients with Rheumatoid Arthritis, Ankylosing Spondylitis and Psoriatic Arthritis in the context of PlanServ was shown to have been a safe and effective measure that brought an extremely important savings (28%) of this health system.
Introduction (Context)

In 2017 Brazil had a population of 207.7 million according to IBGE\(^5\) (Brazilian Institute of Geography and Statistics). Although all population has access to the Public Health System (SUS), the deficient assistance of this system fosters the need for complementary or supplementary health systems in order to ensure greater access to procedures and technologies of which the SUS does not offer.

This supplementary health care system in Brazil is regulated by a government agency, the National Supplementary Health Agency (ANS). According to ANS\(^6\), in April 2018, 47.3 million Brazilians had a medical-hospital plan (supplementary health care system).

Some Brazilians (public employees and their dependents) use other complementary health systems. The body that represents them is the National Council of Health Entities of Public Servants (CONESSP). According to CONESSP\(^7\), 13 million users have complementary public systems (not linked to the ANS agency).

Planserv\(^8\) - Health Care System for State Public Employees, is a complementary health system that falls within the latter classification. It is a public legal system whose management and administration is carried out directly by the state government of Bahia, but which uses (contracted) a private healthcare providers. In March 2018, Planserv had a population of approximately 500 thousand beneficiaries.

The scope of coverage and access to Planserv's health procedures is regulated by Law and State Decree\(^9\). In this context, the Pharmaceutical Assistance and Medication Support Program assures and regulates the coverage of high-cost therapies for the pathologies: Rheumatoid Arthritis\(^11\), Ankylosing Spondylitis\(^12\), Psoriatic Arthritis\(^13\), among others.

In the context of the Pharmaceutical Assistance and Medication Support Program, high-cost therapies for rheumatological diseases are offered, such as "Biological therapy" cases (monoclonal antibodies, Tyrosine Kinase Inhibitors, Fusion Protein, etc.). Biological therapy has greatly improved the management of patients with such diseases, thus increasing the use of these agents. However, the high costs of these medicines make access to these therapies difficult, as well as greatly burdening the health system.
Infliximab (a chimeric "anti-TNF" monoclonal antibody) was the first monoclonal antibody approved in Brazil for the treatment of Rheumatoid Arthritis (RA), Psoriatic Arthritis (PA) and Ankylosing Spondylitis (AS), (among other conditions not covered by Planserv's drug support program) is the biological one most used by the population of patients of these three pathologies in our scenario.

The product REMSIMA was officially approved in Brazil as "Biological Product" (since the Brazilian Health Surveillance Agency [ANVISA] does not recognize the term Biosimilar), published in the “Diário Oficial da União” of April 27, 2015.

Remsima has been approved in Brazil for the following therapeutic indications: Rheumatoid Arthritis, Ankylosing Spondylitis, Psoriasis, Psoriatic Arthritis, Adult Crohn's Disease, Pediatric Crohn's Disease, Fistulizing Crohn's Disease, Colitis, and Ulcerative Colitis.

The approval of REMSIMA for Rheumatoid Arthritis was obtained by the COMPARABILITY approval route, according to Article 46 of Normative Resolution (RN) 55 of December 16, 2010. According to this resolution, the biosimilars approved by comparability in addition to the demonstration of the usual chemical characteristics and good manufacturing practices, require specific clinical studies that can demonstrate equivalence or non-inferiority to the reference product. The other indications were approved by extrapolation (although later studies have reaffirmed their efficacy and safety for all indications approved in the package insert).

In a phase III study (PLANETRA¹ study) involving 606 patients, Remsima reached its main therapeutic equivalence objective with its reference product Infliximab - Remicade ®. The study showed that, after 30 weeks of treatment, 73.4% of patients receiving Remsima achieved 20% improvement (ACR 20) in Rheumatoid Arthritis (RA) symptoms compared to 69.7% of those treated with Remicade.

In the same study, 42.3% of patients in the Remsima group had an improvement in symptoms of Rheumatoid Arthritis greater than or equal to 50% (ACR 50) compared to 40.6% of those treated with Remicade. The safety and tolerability profile also demonstrated Remsima's equivalence to Remicade (information based on American College of Rheumatology Criteria).

After the analyzes of safety and efficacy, Planserv's technical team approved the incorporation of the drug REMSIMA in its medicines list as from July 01, 2016.
Despite the merger, there was no adherence to the use of REMSIMA in the Planserv scenario. The main reason for the lack of adherence was due to economic reasons.

Between August and September 2016, having evaluated the equivalence between the presentations of the reference biological and the biosimilar, and being convinced even of the possibility of exchange of the presentations (interchangeability), and based on internal politics of the institution, that guides the price standardization for equivalent products, Planserv decided to standardize the value of both Infliximabe presentations (Remicade and Remsima).

Our initial expectation was that Janssen (Remicade-producing pharmaceutical industry) would be able to offer its product, at the new price set, to the providers who attended Planserv's patients. However, this did not occur, requiring a change in the use of Remicade for Remsima in all patients who were using this therapy.

Despite having received a formal statement from a single provider, contrary to the exchange of the drug, we were confident that this change would not harm patients. This is because, studies have shown that the interchangeability between Remicade and Remsima did not show significant differences in efficacy or adverse reactions among the groups of patients who used only the reference drug in relation to the groups that performed the alternation.

INTERCHANGEABILITY can be described as the characteristic that ensures the exchange or switching between drugs without increasing safety risks or reducing effectiveness compared to the continued use of the reference product. In biosimilar cases, this characteristic can be measured by the failure of the therapy, by adverse effects, and by the measurement of anti-drug antibodies.

Usually the study designs to evaluate interchangeability are: TRANSITIONAL study (when patients switch from a reference biological product to biosimilar), a SINGLE EXCHANGE study (when patients who were using the reference product switched to biosimilar, and the patients who were using the biosimilar exchange for the reference) and MULTIPLE CHANGES study (when patients perform a series of changes, alternating between the reference biological and the biosimilar).

The PLANETRA EXTENSION² study showed that in patients with RHEUMATOID ARTHRITIS the rate of Antibodies against these biologicals (ADA) showed no difference between the groups.
The PLANETA EXTENSION study on ankylosing spondylitis showed that "ADA positivity rates were comparable between groups (week 102: 23.3% vs. 27.4%). The authors of this same study conclude: "This is the first study to show that switching from PR to its Biosimilar CT-P13 is possible without negative effects on safety or efficacy in patients with AS. In the maintenance group, CT-P13 was effective and well tolerated for more than two years of treatment."

The NOR-SWITCH study also showed that the worsening (activity increase) of the disease, the levels of anti-drug antibodies and adverse effects were equivalent in both the reference and biosimilar Infliximab arms.

The publication of the DANBIO records showed that in 802 patients with arthritis treated with reference Infliximab (with a median> 6 years), a national (non-medical) change to CT-P13 (biosimilar) had no negative impact on disease activity.

An Italian study demonstrated that the switch from the innovator to INX Biosimilar in this cohort to Sodium-arthrits was not associated with any statistically significant differences in efficacy, adverse events or level of anti-drug antibodies. This change (interchangeability) was carried out for drug-economic reasons and backed by law (Tuscany Law No. 450 of 7 April 2015).

A review of the literature carried out precisely to answer what expectations regarding safety, in particular the immunogenicity in the exchange of Remicade by Biossilil, concludes that "although prudent switching practices should be used, the increasing safety experience accumulated so far with CT-P13 and other Biosimilars is favorable and raises no specific concerns."

For all these reasons, we have maintained the value standardization of Remsima and Remicade in our medication table. This action led healthcare providers to exchange the reference Infliximabe for its biosimilar. With this, the patients who were using REMICADE immediately changed to REMSIMA.
Proposal / Objective.

The purpose of this study was to prospectively monitor this cohort of patients in the Planserv Medication Support Program who were in treatment for Rheumatoid Arthritis (RA), or Ankylosing Spondylitis (AS) or Psoriatic Arthritis (PA), who were using Infliximab Reference (REMICADE) and who switched to Biosimilar Infliximab (REMSIMA) for a period of 12 months in order to observe discontinuation of therapy, for all causes. The economic impact of this change was also analyzed.

Method.

This is a prospective, uncontrolled, prospective cohort study with adult patients in the Planserv Medication Support Program, diagnosed with Rheumatoid Arthritis (RA), Psoriatic Arthritis (PA), and Ankylosing Spondylitis (AS), in treatment with the reference Infliximabe - Remicade and who switched to Infliximabe Biosimilar - Remsima, in August 2016. These patients were followed between September 2016 and September 2017.

The primary endpoint analyzed was the discontinuation of all-cause treatment (with particular interest in therapeutic failure). The outcome was considered to be intention-to-treat, therefore any patient who was already on REMICADE therapy and who received at least one dose of REMSIMA was entered into the study.

In case of discontinuation of the drug the prescribing physician was asked to register the reason. Information on the patient's clinical status during the course of the study was also recorded by the attending physician.

Reference period: Because the study was transitional and we did not have a comparator arm, it was necessary to set a reference value so that we could compare the "Therapy Discontinuation Rate" found in the study. This reference value was defined by the same Therapy Discontinuation Rate evaluated in patients from the same programs (Rheumatoid Arthritis, Ankylosing Spondylitis and Psoriatic Arthritis) one year before the study. Therefore, we retrospectively assessed the rate of discontinuation of therapy from these patients when they were using REMICADE between September 2015 and August 2016.
Table 1 below schematically shows the study design and sampling, with inclusions and exclusions, of the reference period and the intervention period.

TABLE 1: DESIGN AND SAMPLE OF THE STUDY

As can be seen in TABLE 1, in the reference period 10 (11%) patients discontinued therapy, of these 08 (9%) patients had failed therapy and switched the protocol to another biological and 02 (2%) patients discontinued therapy without return to the program.

We observed that the rates of discontinuation of Infliximab therapy presented in the pivotal studies (which approved the biosimilar) were higher than the numbers found in our reality, either with patients who were using REMICADE, as well as patients who started using REMSIMA. Table 2 below shows the rates (and reasons) for discontinuation in these studies.
As observed in TABLE 01, during the intervention period, 81 patients were in the medication support program, using Infliximabe reference (REMICADE). Of these 78 patients switched to Biosimilar Infliximab (REMSIMA), and were included in the study. Three patients remained receiving REMICADE by judicial injunction. As there was no exchange of the reference Infliximab for biosimilar, these patients were excluded from the study. A parallel follow-up showed that these three patients used REMICADE by the end of follow-up study in September 2017.

In the reference period, two patients were excluded. One of them was a patient who was receiving REMICADE by judicial injunction for an Off Label indication (Behçet's Disease). As it was not a pathology predicted in the study proposal, this case was excluded.

A second patient started biological therapy in August 2016. Of the three doses of induction, he used only the first dose of REMICADE, and the next with REMSIMA. Having used the REMSIMA to date follow up of this study. However, considering that the patient had only received a single dose of REMICADE, it would not be possible to evaluate the impacts of an "exchange" of the reference drug for its biosimilar.

The secondary endpoint analyzed was a register of "Increase in Disease Activity", represented by an increase in the usual control scores.

<table>
<thead>
<tr>
<th>Trials</th>
<th>Planeta</th>
<th>Planeta Extension</th>
<th>Planeta</th>
<th>Planeta Extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reason for Discontinuation</td>
<td>Remsima</td>
<td>Remicade</td>
<td>Remsima</td>
<td>Remicade</td>
</tr>
<tr>
<td>By all causes</td>
<td>22,8%</td>
<td>27,0%</td>
<td>15,8%</td>
<td>11,1%</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>11,9%</td>
<td>15,8%</td>
<td>10,1%</td>
<td>5,6%</td>
</tr>
<tr>
<td>Suspension of Consent</td>
<td>5,3%</td>
<td>6,9%</td>
<td>2,5%</td>
<td>3,5%</td>
</tr>
<tr>
<td>Lack of effectiveness</td>
<td>3,3%</td>
<td>2,0%</td>
<td>0,6%</td>
<td>0,7%</td>
</tr>
<tr>
<td>Violation of the Protocol</td>
<td>1,0%</td>
<td>1,0%</td>
<td>0,0%</td>
<td>0,0%</td>
</tr>
<tr>
<td>Loss of Follow-up</td>
<td>0,0%</td>
<td>0,7%</td>
<td>1,3%</td>
<td>1,4%</td>
</tr>
<tr>
<td>Death</td>
<td>0,0%</td>
<td>0,3%</td>
<td>0,6%</td>
<td>0,0%</td>
</tr>
<tr>
<td>Researcher’s Decision</td>
<td>0,0%</td>
<td>0,3%</td>
<td>0,6%</td>
<td>0,0%</td>
</tr>
<tr>
<td>All Causes Less Adverse Effect</td>
<td>10,9%</td>
<td>11,2%</td>
<td>5,7%</td>
<td>5,6%</td>
</tr>
</tbody>
</table>
The parameters used for clinical analysis took into consideration the protocol of Planserv institution (which in turn takes into account international protocols). The evaluation scores to measure the clinical worsening or indicator of disease activity were the same used by the attending physician (SDAI for Rheumatoid Arthritis patients, BASDAI for Ankylosing Spondylitis and CASPAR for Psoriatic Arthritis).

All patients had their disease activity scores measured at the time of REMICADE exchange by REMSIMA. This measure was considered in our study as ZERO MONITORING (M0). These patients had their scores recalculated 3 times over the 12 months of monitoring, according to the attending physician himself (and checked by Planserv's technical auditing team). FIRST MONITORING (M1) after drug replacement occurred approximately 3 months after M0 (ranging from 2 to 6 months). SECOND MONITORING (M2) occurred approximately 7 months after M0 (ranging from 4 to 10 months). THIRD MONITORING (M3) occurred approximately 9 months after M0 (ranging from 6 to 13 months).

"Increased Disease Activity" was considered to be any patient who, in one of the three measures (M1, M2 or M3) presented elevation of the score in relation to M0, and that the value of the score was higher than the limit of disease REMISSION (this limit was considered SDAI 5 for Rheumatoid Arthritis and BASDAI 4 for Ankylosing Spondylitis). Considering the qualitative aspect of the CASPAR score, for patients with Psoriatic Arthritis, it was considered "Increase in Disease Activity" in any one of the three measures that presented elevation of the score in relation to M0, regardless of the limit of remission.

For the evaluation of the secondary endpoint, in order to define a study reference rate for the "increased disease activity", we collected retroactively the values of the standard scores (SDAI, BASDAI and CASPAR) in 12 months (September 2015 to August 2016 - reference period) exclusively from the same patients (78) while using REMICADE.

The scores recorded 12 months prior to the change of REMICADE by REMSIMA were considered ZERO CONTROL (C0). In the same way, we collected the scores recalculated 3 times over the 12 months (C1, C2 and C3), using the same methodology used to monitor the activity of the disease after the reference Infliximab was replaced by biosimilar.
This strategy (to measure the increase in disease activity) seemed to us to be more adequate and fair, since the same method was used before and after the exchange of Infliximab in the same patient group. The data on increased disease activity used in pivotal studies used parameters that were not available to our team (such as ADA or AMA antibody to the drug). For this reason, the pivotal study indicators were not used as indicators of increased disease activity in our study.

The instrument for collecting the data was the form "Therapeutic Protocol\textsuperscript{11,12,13}", a mandatory document filled out by the patient’s attending physician under the Medication Support Program, sent monthly to Planserv, so that the drug can be authorized. Eventually, contacts were made with Planserv’s technical staff with attending physicians and patients, to collect information and clarify doubts.

A minimum follow-up period was established for each 12-month patient. However, the entire study period was 13 months, since a small group of patients (accompanied by the provider who initially challenged our measure) performed the drug replacement one month late for the others.

Finally, an economic analysis of cost minimization was also conducted, since we already assumed that the clinical outcomes were equivalent. As well, considering that the other costs of infusion and follow-up are equally equivalent, since they use the same structure and resources. The analysis of cost minimization was summarized in the comparative analysis of cost "drug-to-drug”.

**Results**

78 patients who were taking REMICADE and exchanged for REMSIMA were followed, of these 38 patients had Rheumatoid Arthritis, 32 patients with Ankylosing Spondylitis, and 8 patients with Psoriatic Arthritis.

**TABLE 3: PATIENTS CHARACTERISTICS INCLUDED IN THE STUDY.**

<table>
<thead>
<tr>
<th></th>
<th>All n (%)</th>
<th>RA n (%)</th>
<th>AS n (%)</th>
<th>PA n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>78 100%</td>
<td>38 49%</td>
<td>32 41%</td>
<td>8 10%</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>46 59%</td>
<td>32 84%</td>
<td>8 25%</td>
<td>6 75%</td>
</tr>
<tr>
<td>Male</td>
<td>32 41%</td>
<td>6 16%</td>
<td>24 75%</td>
<td>2 25%</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 – 50 years</td>
<td>26 33%</td>
<td>8 21%</td>
<td>17 53%</td>
<td>1 13%</td>
</tr>
<tr>
<td>51 – 80 years</td>
<td>51 65%</td>
<td>29 76%</td>
<td>15 47%</td>
<td>7 88%</td>
</tr>
<tr>
<td>81 – 100 years</td>
<td>1 1%</td>
<td>1 3%</td>
<td>0 0%</td>
<td>0 0%</td>
</tr>
</tbody>
</table>
Primary Outcome Analysis: Out of the total sample, 5 (6.4%) patients discontinued therapy with REMSIMA (04 [5.1%] patients had failed therapy and switched protocol to another biological and 01 [1.3%] if discontinued) therapy with no return to the program - loss of follow-up).

Analysis of these patients by subgroup (pathology) showed that 03 (8%) patients had RA. 01 (3%) patient had AS and 01 (13%) had AP.

<table>
<thead>
<tr>
<th>TABLE 4: RESULT - DISCONTINUATION OF THERAPY</th>
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</table>

Considering the reference threshold index previously established for the 11% study, we observed that the REMSIMA discontinuation rate (6.4%) was within the estimated, satisfying expectations.

Of the 05 cases that discontinued therapy with REMSIMA, 04 were due to therapeutic failures, followed by protocol change (biological change). Of the 10 cases that discontinued therapy with REMICADE, 08 were due to failure and followed by protocol change (biological change). All 08 cases who failed therapy with REMICADE were carriers of Rheumatoid Arthritis.

The subgroup analysis (by pathology) also showed equivalence between the results found in REMSIMA compared to REMICADE. In Rheumatoid Arthritis, the REMSIMA therapy discontinuation rate was 8%, whereas REMICADE therapy was 18%. In Ankylosing Spondylitis the rate of discontinuation of therapy was exactly the same (3%) among patients who used REMSIMA or REMICADE. In Psoriatic Arthritis, there was no case (0%) that had discontinued therapy among REMICADE patients, while the discontinuity rate among REMSIMA patients was 13%. However, it is important to remember that these 13% equals only one patient. The very low sample number among patients with Psoriatic Arthritis is certainly a confounding factor. However, the data seems sufficient to recognize the equivalence of results between REMICADE and REMSIMA, also in the subgroup analyzes (by pathology).
An interesting find deserves comment. One patient in the subgroup of RA who was considered "Therapeutic Failure" had been using REMICADE and was not showing satisfactory improvements. The attending physician informed that he would make one last attempt, with another 3 months of REMICADE and if there was no satisfactory answer, he would exchange it for another biological. This patient received one more dose of REMICADE, and at this time the exchange by REMSIMA occurred. The patient received a single dose of REMSIMA, and as she was not showing improvement the attending physician indicated the change to GOLIMUMABE. By clinical criteria, neither we nor the attending physician was assigned the "Therapeutic Failure" to Remsima, however for the purposes of this study, how the outcome was measured by the "Intention to Treat", and how the patient received a dose of REMSIMA, the case was counted as "Therapeutic Failure".

Analysis of Secondary Outcome (Increased Disease Activity):

Of the entire sample of patients who underwent REMICADE replacement by REMSIMA, 92% had the four measures (M0-M1-M2-M3) calculated over 12 months (91.4% of patients with RA-94, 5% of patients with AS - 81.3% of patients with AP).

In the control period (when patients were still using REMICADE), 96% of the patients had the four (C0-C1-C2-C3) measures of calculated scores (96.1% of patients with RA - 95.3% of patients with AS - 96.9% of patients with AP).

The records of disease activity of both periods (intervention and reference) are recorded in TABLE 05 below.

<table>
<thead>
<tr>
<th>DATA OF CLINICAL EVOLUTION</th>
<th>All (%)</th>
<th>RA (%)</th>
<th>AS (%)</th>
<th>PA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>REMSIMA</td>
<td></td>
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</tr>
<tr>
<td>Everyone who made the switch</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable</td>
<td>78 100%</td>
<td>38 49%</td>
<td>32 41%</td>
<td>8 10%</td>
</tr>
<tr>
<td>Record of increase in disease activity</td>
<td>45 58%</td>
<td>17 45%</td>
<td>24 75%</td>
<td>4 50%</td>
</tr>
<tr>
<td>REMICADE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everyone who made the switch</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable</td>
<td>78 100%</td>
<td>38 49%</td>
<td>32 41%</td>
<td>8 10%</td>
</tr>
<tr>
<td>Record of increase in disease activity</td>
<td>42 54%</td>
<td>14 37%</td>
<td>24 75%</td>
<td>4 50%</td>
</tr>
</tbody>
</table>
As can be observed, the results found for the index of increase in disease activity were: from the total sample of patients who underwent REMICADE change by REMSIMA, 42% presented during the study, at least ONE increase in disease activity in the follow-up period of the 12 months that the REMSIMA used (intervention period). In the control period (reference), which used REMICADE, the percentage of patients presenting at least ONE increase in disease activity was 46%.

Subgroup analyzes (by type of pathology) indicated that:

- Of the patients with RA, 55% of the patients presented, at some point, a record of at least ONE increase in disease activity in the 12-month follow-up period that used REMSIMA (period of intervention). In the period that used REMICADE (referência), the rate of increase in disease activity in this same subgroup of patients was 63%.
- Of the patients with AS, 25% of the patients presented at some time a record of at least ONE increase in disease activity in the period that used REMSIMA (period of intervention). The same index (25%) showed the patients who used REMICADE (período de referência).
- Of the patients with PA, 50% of the patients presented at some time a record of at least ONE increase in disease activity in the period that used REMSIMA (period of intervention). The same index (50%) showed the patients who used REMICADE (período de referência).

The results found in the index of increased activity of the disease, demonstrate that it is quite frequent that patients with these diseases present, during their evolution, periods where they register some elevation of the scores, demonstrating an increase in the activity of the disease. However, this elevation is not always accompanied by relevant symptoms and does not always reflect a real clinical worsening. Factors external to the underlying disease (such as infectious processes for example) may raise these scores and are not directly related to worsening of the underlying disease.

This statement is based on the high rate of increase in disease activity as opposed to low rates of therapeutic failure. For, despite the fact that many patients had a possible increase in their scores, for the vast majority of them, it was not necessary to change the biological or even dose adjustments of the drug.
However, the most important of this finding is that the rates of increased disease activity found during the period of use of REMSIMA were equivalent to those found in the period of use of REMICADE for the same patient population. Demonstrating that the exchange of the reference Infliximab for its biosimilar did not aggravate the rate of increase of disease activity.

ECONOMIC ANALYSIS (COST MINIMIZATION):

As already mentioned, Planserv approved the incorporation of the drug REMSIMA in its medication list as of July 2016, with the presentation "Remsima - 01 vial containing lyophilized powder for concentrated solution of 100 mg for venous infusion.

The value of the light bulb of the REMSIMA represented at the time R $ 2,679.66 reais (US $ 845.96 Dollars - Quotation of the Commercial Dollar at Sale of 09/30/2017 - Source THOMSON REUTERS10).

At the same time, REMICADE included in our table "Remicade - 01 vial containing lyophilized powder for concentrated solution of 100 mg for venous infusion, valued at R $ 3,715.65 reais (US $ 1,173.02 Dollars - Quotation of the Commercial Dollar on Sale of 09/30/2017 - Source THOMSON REUTERS10).

With the standardization of values, both Infliximabe presentations (reference and biosimilar) now have a single price of R $ 2.679,66 reais (US $ 845.96 Dollars - US Dollar Commercial Price on Sale / 2017 - Source THOMSON REUTERS10).

During the period from September 2016 to September 2017, Planserv approved 1,689 ampules of REMSIMA (since the pharmaceutical industry producing REMICADE did not guarantee to suppliers the reduction of the value realized by Planserv).

<table>
<thead>
<tr>
<th></th>
<th>Value (R$) 1 vial</th>
<th>Value (R$) 1689 vials</th>
</tr>
</thead>
<tbody>
<tr>
<td>REMSIMA</td>
<td>R$ 2.679,66 (US$ 845,96)</td>
<td>R$ 4.525.945,74 (US$ 1.428.824,90)</td>
</tr>
<tr>
<td>ECONOMY</td>
<td>R$ 1.035,99 (US$ 327,06)</td>
<td>R$ 1.749.787,11 (US$ 552.401,54)</td>
</tr>
</tbody>
</table>

Cotação do Dólar Comercial a Venda de 30/09/2017 – Fonte THOMSON REUTERS10.
The impact of the incorporation of REMSIMA and the standardization of REMICADE based on the value of REMSIMA generated savings of approximately 28% with this product alone, equivalent to more than R $ 1.75 million in the period evaluated (with savings monthly average of R $ 134,599.01).

**CONCLUSION**: This prospective, real-world cohort demonstrated that the transition from the reference Infliximab to REMICADE by its biosimilar REMSIMA in the 78 patients of the Planserv drug support program was presented as a safe, effective, equivalent measure to the reference product and brought an extremely significant savings to the health system. We understand that measures like this, which ensure the same clinical efficacy and safety, associated with a significant cost reduction, reflect in an allocative efficiency of the health resource. Actions such as this should be pursued by managers of health institutions, especially public institutions such as Planserv.
References:


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22. A Nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1–year clinical outcomes from the DANBIO registry. Bente Glintborg, Ann Rheum Dis published online May 4, 2017