BIOLOGICALS AND SWITCH IN RHEUMATOID ARTHRITIS THROUGHOUT TIME – ARE WE BEING MORE AGGRESSIVE?

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Abstract

Objectives: To investigate the switches performed in patients with rheumatoid arthritis under biological therapy and specifically comparing the switches from earlier days with more recent switches.
Patients and methods: Patients with rheumatoid arthritis under biological therapy followed at Hospital Garcia de Orta, Almada, and included in the Rheumatic Diseases Portuguese Register (Reuma.Pt) were included in this study. Switches occurring before and after January 2007 were compared with respect to patients' demographic and clinical characteristics, such as disease activity and duration of biological therapy. The survival of the first biological agent was compared between patients starting biological therapy before and after 2007. EULAR response and remission rate at the last evaluation were calculated. Comparisons between groups were established using a t-test or chi-square, as appropriate. Survival curves of the first biological were compared through the logrank test.
Results: In total, 123 patients were included in the analysis (mean age 57.0 ± 13.1 years and mean disease duration 11.7 ± 8.0 years). A total of 85 switches were documented, 20% of which took place before 2007. Comparing the switches before and after 2007, the latter were registered among older patients (recent switches 56.2 ± 12.9 years *vs* older switches 48.9 ± 11.0 years, p=0.04) and with a shorter duration of the first biological agent (recent switches 461.9 ± 293.2 days *vs* older switches 773.7 ± 475.8 days, p=0.03). No further significant differences were found, including the disease activity. The survival of the first biological was shorter in patients starting biological therapy after 2007 (2949 days for biological onset before 2007 and 818 days for onset after 2007, p <0.001). A good EULAR response was achieved by 19% and 30% of the patients, before and after 2007, respectively (p = 0.23). Remission was achieved by 14% and 22% of the patients, before and after 2007, respectively (p = 0.30).
Conclusions: Switches were more frequently performed in more recent years, in older patients and with a shorter duration of biological therapy. A trend towards a better and more targeted control of the disease could be discussed in light of our results. Although switches were more frequently performed in more recent years, in older patients and with a shorter duration of biological therapy, there is still room for improvement when aiming at remission, for example by applying a tighter therapy strategy like the "treat to target model".

Keywords: Rheumatoid Arthritis; Biological Therapy; Drug Switching; Registries; Portugal.

Introduction

In the last decade, biological therapies have dramatically changed the treatment of rheumatoid arthritis (RA) in such a way that remission is currently an achievable goal. This goal has been advocated by recent initiatives, namely the *Treat to Target*[1] and the EULAR recommendations for the management of RA[2], as attaining a state of remission or low disease activity leads to better structural and functional outcomes than allowing residual disease activity[3,4], and the earlier the remission state is achieved the better it is[1]. Both initiatives recom-

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mend that patients should be followed meticulously and existing therapy should be intensified or ultimately changed for another one until the target is achieved: remission[1,2]. With respect to biological therapy in RA, a "cycling for remission" approach has recently been proposed: start with an effective agent; move to another effective agent unless persistent remission is achieved with acceptable toxicity; consider going back to the most effective agent if none of the biological disease modifying anti-rheumatic drugs (DMARDs) results in remission[5]. This proposal is presented in light of the evidence reflected in the EULAR recommendations for the management of RA[2], and the process can develop at a relatively fast pace, as a patient's response to treatment during the first 3 months of biological therapy is known to determine the level of disease activity at 1 year[6].

For several years, inhibitors of TNF (etanercept, infliximab, and adalimumab) and anakinra have been the only option available for patients failing synthetic DMARDs. Recently, biological agents with novel mechanisms of action (rituximab, abatacept, and tocilizumab) have been approved for use in patients with RA and, even more recently, the armamentarium of biological agents has been enriched through the approval of new TNF inhibitors, golimumab and certolizumab pegol. The diversity of biological agents increases the possibilities of switching therapies and consequently of achieving successful treatment response. Patients may fail to achieve the target with one medication, for instance, a TNF inhibitor, but then may respond very well to another medication with an identical[7, 8] or different mechanism of action[9-11]. Consequently, rheumatologists' clinical practice is expected to have been adapted, throughout this decade, to a more intensified treatment strategy and to a better and more targeted control of the disease. A more aggressive attitude towards RA therapy, more specifically involving biological therapy, is therefore expected. Hence, it is interesting to reflect upon our daily clinical practice and to analyze how we are dealing with switches. The aims of the present study were to investigate the switches performed in patients with RA under biological therapy and to compare older switches (i.e. performed in earlier days) versus more recent switches and the circumstances in which these took place, as well as to evaluate the survival of the first biological. Aiming at higher response levels as we currently do, we would expect to identify, comparing to earlier days, a higher number of switches currently being performed, a lower disease activity value before a switch and a shorter survival of the first biological agent.

Patients and methods

Study population

Data from the Rheumatic Diseases Portuguese Register, Reuma.pt, more specifically the register of patients with RA receiving biological therapies (BioRePortAR) and the subset from Hospital Garcia de Orta, Almada, has been used. Reuma.pt has been described in detail elsewhere[12]. In summary, this electronic register was launched in 2008 and continuously includes patients from several Portuguese Rheumatology departments. Inclusion criteria are RA, diagnosed according to the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) criteria[13] and start of biological therapy. Data from the previous years, from the introduction of biologicals in 2000 until 2008, have been collected on paper and later were entered into the electronic register; these data have been systematically collected according to a standardized, published protocol, which contained the same items as the ones included in the electronic register[14]. Reuma.pt is also used as an electronic patient chart and, therefore, the frequency of observations of the patients is not pre-determined. Assessments are made by rheumatologists, in general every 3-4 months, and include clinical information, such as the monitoring of disease activity (Disease Activity Score with 28-joint assessment – DAS28[15]), medication, adverse events, and comorbidities. Function is monitored through the Health Assessment Questionnaire (HAQ) once a year[16]. Demographic and other clinical characteristics, including health habits and previous medication, are collected at the onset of biological therapy. Data from all patients exposed to biologicals from 2001 to 2011 were used. Data refer to usual clinical practice, without any intervention on the decisions of the rheumatologists. Patients with missing information at baseline, i.e. evaluation corresponding to the start of the first biological, were not included in the analysis, in order to require all the patients to have a complete follow-up while on biological therapy and to assure completeness of the information on switches.

Switch assessment and subcohorts

A switch of biologicals was defined as the start of a subsequent biological, independently of the reason of discontinuation of the previous one. In order to investigate the current practice with respect to switches and to compare our earlier practice in terms of switches with our more recent clinical practice, a time cut-off was necessary. We decided to establish the cut-off as of January 1st 2007, with the following reasoning: 1) it divided the total period (2001-2011) in approximately balanced parts in terms of number of patients starting a first biological therapy in each of them; 2) in 2007, the Portuguese guidelines for the use of biologicals in RA were updated by the RA Study Group (GEAR) of the Portuguese Society of Rheumatology[17]. In these guidelines, the criteria for introduction and maintenance of biologicals were discussed, as well as the contraindications and procedures in case of inadequate response.

Taking the cutoff of 2007 into account, three subcohorts of patients could be identified: subcohort 1 – patients starting the first biological in the period of 2001-2006 and being followed-up during the same period (2001-2006); subcohort 2 – patients starting the first biological in the period of 2001-2006 and being followed-up in the period of 2007-2011, actually including the same patients as subcohort 1, but in a later follow-up period, and only excluding patients with a definitive discontinuation of biological therapy in the follow-up period of 2001-2006; subcohort 3 – patients starting the first biological in the period of 2007-2011 and being followed-up in this period. Each of these subcohorts was analyzed in terms of demographic and clinical characteristics of the patients, including initial and final levels of DAS28 (calculated with the erythrocyte sedimentation rate) and HAQ, number of switches, ratio of switches per number of patients on biologicals, number of first switches, disease duration and time under biological exposition.

Switches before 2007 were designated as older switches and switches after 2007 as recent switches. Older and recent switches were compared with respect to demographic and clinical characteristics of the patients at the evaluation immediately before the switch, as this was considered the evaluation where the rheumatologist actually made the decision about the switch. Clinical characteristics compared were disease duration, time under biological exposition, disease activity (as measured by the DAS28), function (as measured by the HAQ), concomitant therapy with corticosteroids, concomitant therapy with methotrexate, and duration of first biological at first switch. Because recent switches included both switches in patients who started biological therapy before and after 2007, a more pure comparison between older and recent switches was also performed, in which only the recent switches of patients who had started their first biological after 2007 (i.e. belonging to the subcohort 3) where compared to older switches (subcohort 1).

Furthermore, the survival of the first biological was evaluated through means of assessing its survival time for half of the patients and comparing the survival between patients starting their first biological before and after 2007.

Disease activity control

A possible way to assess the effectiveness of optimal and targeted disease activity control and of the approach to switches throughout time is to evaluate its effect, more specifically the disease activity control achieved at the last evaluation of the total population and stratified by each subcohort. Disease activity control was considered to be evaluable when the DAS28 was available at the last evaluation of each subcohort. For the purpose of this assessment, patients starting a new biological or awaiting a switch at their last evaluation, or who had discontinued biological therapy permanently were not included, as the disease activity control could not be properly evaluated in these cases. Remission achieved at the last assessment, as defined by a DAS28<2.6[18], was also determined.

For all the patients with an available DAS28 both at baseline and at the last evaluation, the EULAR response was calculated[19], both for the total population and also split by each subcohort.

Statistical analysis

Continuous variables are presented as means ± standard deviations, and categorical variables as frequencies.

Comparisons were established between different groups. Continuous variables were compared using an independent two-samples *t*-test adjusted for heterogeneity of variances, as appropriate. Categorical variables were compared using the chi-square test.

The survival of the first biological was assessed through means of a survival analysis and the sur-

vival curves for patients starting their first biological before and after 2007 were compared by a log-rank test.

Statistical analysis was performed assuming a 5% significance level and using STATA SE 10.

Results

A total of 123 out of 159 patients with RA who have been treated with biological therapy at the Hospital Garcia de Orta were included in this analysis. Eight patients were not included because information was only available from recent evaluations and not from the first years of follow-up. The remaining 28 patients have been on biological therapy at some point throughout the follow-up period (16 pertaining to the 1st subcohort, 5 to the 2nd, and 7 to the 3rd subcohort), but have been definitely discontinued, mainly due to adverse events, others due to loss to follow-up or transfer to another hospital, and their information was no longer available.

The demographic and clinical characteristics of the included population are summarized in Table I. The majority of the patients were on a TNF inhibitor as a first biological (33% infliximab, 32% etanercept, 20% adalimumab), followed by tocilizumab (7%) and anakinra (2%).

Table II shows the characteristics of each of the subcohorts stratified according to the date of onset of biological therapy and the follow-up period. A total of 56 patients started their first biological in the period of 2001-2006 and the same patients were followed-up in both periods (2001-2006 and 2007--2011). A total of 67 patients were started on a biological in the period 2007-2011. Patients from the subcohorts 1 and 3, starting a biological before and after 2007, respectively, had similar demographic and clinical characteristics, except for the age at onset of first biological, which was higher in the group of patients who started their first biological in the period of 2007-2011 (55 years old *vs* 50 years old).

With respect to the switches, fifty-eight patients (47%) had their biological therapy switched at least once (Table I). A total of 85 switches were registered, of which 17 (20%) in the 1st subcohort (Table II). In total, 68 switches were of recent onset (i.e. taking place after January 2007), of which 32 (47%) in patients who had started their first biological before 2007. Comparing subcohorts 1 and 3 (i.e. starting their first biological before and after 2007),

Table I. Demographic and clinical characteristics of the population

	Mean ± SD or n (%) (N = 123)
Current age (years)	57.0 ± 13.1
Female gender (%)	106 (86%)
Disease duration (years)	11.7 ± 8.0
Time under biological exposition (years)	4.4 ± 2.8
Rheumatoid factor positivity (%)	81 (66%)
ACPA positivity (%)	86 (70%)
Number of patients with at least one switch (%)	58 (47%)
Number of biologicals per patient	1.72 ± 0.95
Frequency of number of biologicals per patient (%):	
• 1	63 (51%)
• 2	40 (33%)
• 3	15 (12%)
• 4	4 (3%)
• 7	1 (1%)

there was an increase in the number of switches, with a ratio of switches per number of patients under biologicals of 30% in subcohort 1 and of 54% in subcohort 3 ($p = 0.02$). A tendency towards a lower disease activity level at baseline and at the final evaluation was found throughout time, but the difference between subcohorts 1 and 3 was not statistically significant.

Table III shows the comparison between switches of older and recent onset. Patients with recent switches were found to be statistically significantly older. This difference was also found when the comparison was refined to patients from subcohort 3 only (i.e. starting their first biological in the period of 2007-2011) compared with subcohort 1. Comparing all the recent and older switches, a longer time under biological exposition was found in patients with a recent switch (3.0 years in recent switches *vs* 1.6 in older switches, $p < 0.01$). In patients from subcohort 3, a trend towards shorter biological exposition was found compared with subcohort 1 (1.2 years *vs* 3.0, $p = 0.16$). Patients with a recent switch and who had started the first biological in the period 2007-2011 had a shorter duration on their first biological at the time of their first switch (461.9 ± 293.2 in recent switches

Table II. Demographic and clinical characteristics of the subcohorts stratified by onset of biological therapy and follow-up period

	Cohort 2001-2006	Cohort 2007-2011		
	Follow-up period 2001-2006	Follow-up period 2007 – March 2011		
	Subcohort 1 Mean ± SD or n (%) N = 56	Subcohort 2 Mean ± SD or n (%) N = 56	Subcohort 3 Mean ± SD or n (%) N = 67	p value §
Age at onset of 1st biologic (years)	49.8 ± 12.3		54.7 ± 13.7	0.04*
Female gender (%)	50 (89%)		56 (84%)	0.36
Rheumatoid factor positivity (%)	35 (64%)		46 (69%)	0.10
Disease duration at onset of 1st biologic (years)	6.6 ± 7.2		7.6 ± 8.0	0.46
Number of switches	17	32	36	–
Ratio number of switches/number of patients under biologic (%)	17/56 (30%)	32/56 (57%)	36/67 (54%)	0.02*
Number of first switches	15 (15/17 = 88%)	14 (14/32 = 44%)	28 (28/36 = 78%)	0.08
Ratio number of first switches/ /number of patients under first biologic	15/56 (27%)	14/56 (25%)	28/67 (42%)	0.12
Initial DAS28	5.8 ± 1.2 (n = 50)	4.0 ± 1.4 (n = 48)	5.7 ± 1.2 (n = 66)	0.67
Final DAS28	4.0 ± 1.4 (n = 48)	3.7 ± 1.2 (n = 52)	3.7 ± 1.3 (n = 62)	0.07
Initial HAQ (0-3)	1.6 ± 0.7 (n = 41)	1.0 ± 0.7 (n = 47)	1.5 ± 0.6 (n = 52)	0.67
Final HAQ (0-3)	1.0 ± 0.7 (n = 47)	1.0 ± 0.8 (n = 42)	1.0 ± 0.6 (n = 48)	0.70
Time under biological exposition (years)	2.9 ± 1.8 (n = 56)	4.2 ± 0.3 (n = 56)	4.2 ± 0.1 (n = 67)	<0.01*
Definitive discontinuation of biologics	0	3 (5%)	2 (3%)	–

§Comparison between subcohort 3 and subcohort 1
*Statistically significant difference (*p*-value <0.05)

vs 773.7 ± 475.8 days in older switches, $p = 0.03$). No further significant differences were found between older and recent switches. Interestingly, a slight tendency towards a lower level of DAS28 was noted in recent switches.

The survival of the first biological was shorter in patients who started biological therapy in the period of 2007-2011. The time to 50% discontinuation of the first biological was 2949 days when the first biological was started before 2007, compared to 818 days when the first biological was started in the period of 2007-2011 ($p < 0.001$) (Figure 1).

One hundred and eleven patients were considered evaluable for analysis of disease control, as assessed at the last observation (Table IV). Only patients that had not recently started a new biological, had not been proposed for a switch and had not definitely discontinued biological therapy were included for this analysis. In terms of EULAR response, 53% had a moderate response, 35% a good response and 12% none. A total of 24 patients (22%) were in remission (DAS28 < 2.6).

Dividing the population in the three subcohorts and considering the last evaluation of each of

Table III. Comparison of the disease activity between older and recent switches

	Older switch (before 2007) N = 17+ Mean ± SD or n (%)	Recent switch, all considered (after 2007) N = 68 Mean ± SD or n (%)	p value§	Recent switch only from subcohort 3¶ (after 2007) N = 36 Mean ± SD or n (%)	p value¤
Age (years)	48.9 ± 11.0 (n = 17)	56.2 ± 12.9 (n = 68)	0.04*	56.6 ± 14.1 (n = 36)	0.049*
Disease duration (years)	7.4 ± 4.5 (n = 17)	9.2 ± 7.5 (n = 66)	0.22	7.5 ± 8.6 (n = 34)	0.98
Time under biological exposition (years)	1.6 ± 1.3 (n = 17)	3.0 ± 2.7 (n = 68)	<0.01*	1.2 ± 0.9 (n = 36)	0.16
Duration of first biological at first switch (days)	773.7 ± 475.8 (n = 15)	918.6 ± 932.0 (n = 42)	0.45	461.9 ± 293.2 (n = 28)	0.03*
DAS28 before the switch	5.7 ± 1.3 (n = 14)	5.2 ± 1.6 (n = 64)	0.28	5.7 ± 1.8 (n = 34)	0.91
HAQ (0-3)	1.3 ± 0.5 (n = 8)	1.1 ± 0.8 (n = 26)	0.53	1.2 ± 0.8 (n = 14)	0.65
Corticosteroids (%)	15 (88.2%)	46 (67.7%)	0.09	28 (77.8%)	0.36
Methotrexate (%)	15 (88.2%)	56 (82.4%)	0.60	29 (80.6%)	0.49

+n refers to number of observations/switches; some patients had more than one switch
§Comparison of older *vs* recent switches, all considered
¤Comparison of older *vs* recent switches in subcohort 3 (i.e. patients started on biological in the period of 2007-2011)
¶Subcohort 3 means that patients were started on a first biologic in the period of 2007-2011
*Statistically significant ($p < 0.05$)

them, a trend towards a higher achievement of remission and a better profile of EULAR responses was found in subcohort 2 (i.e. patients starting biological therapy in the period of 2001-2006 and being followed--up in the period of 2007-2011) and subcohort 3 (i.e. patients starting biological therapy in the period of 2007-2011).

Discussion

This study showed a clear increase in the number of switches in patients with RA under biological therapy throughout time, specifically when comparing patients who started biological therapy before and after 2007. Patients with a recent switch were found to be older and had a shorter duration of the first biological compared with patients with a switch before 2007. No significant differences with respect to disease activity before the switch could be demonstrated. The survival of the first biological was shorter in patients who started biological therapy in the period of 2007-2011. A trend towards a better disease activity control, as assessed by the mean final DAS28 score and the EULAR response, was also manifest in the more recent follow-up period (i.e. 2007-2011), when compared to the earlier follow-up period of 2001-2006.

These results suggest a trend towards a better and more targeted disease control of patients with RA under biological therapy throughout time. This goes along with what we expected, with the improvements we have witnessed in RA during the last decade and with the consequent increasing level of demand we have with respect to the disease control. In more recent years, switches were performed at an earlier stage, in terms of the duration of biological therapy, suggesting that rheumatologists were reducing the time to evaluate the effectiveness of a therapy before switching if they were not satisfied with the results. This is also in line with the larger availability of biologicals in recent years, including drugs with a different mode of action. However, disease activity was still considerably high before a switch, and has not decreased significantly throughout time, as one may have expected. One potential

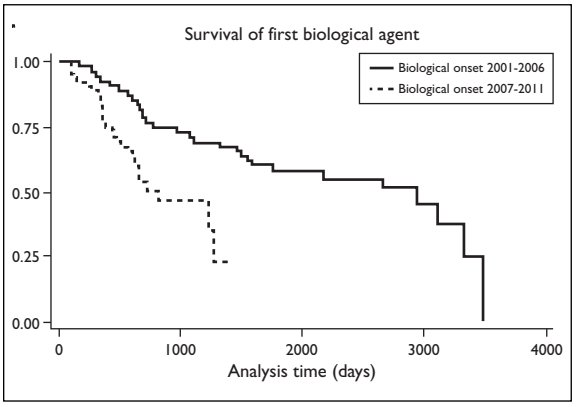

Figure 1. Time to discontinuation of the first biologic agent, stratified by the period for onset of biological therapy

explanation for this is that rheumatologists may be reluctant to switch and still wait a long period before actually changing the biological. This period was on average of 467 days in more recent years, which is around 15 months. There seems to be room for improvement in this aspect.

Another finding was that recent switches were performed in older patients. We would instead expect that patients were started on biological therapy earlier in their disease course and, consequently, in their life. However, this would also be dependent on an earlier referral of patients from their general practitioners to rheumatologists, and actually no difference was demonstrated in the disease duration before a switch. The fact that switches were performed in older patients potentially reflects the increased occurrence of switches that can take place and to a less restrictive group of patients, being in fact generalizable to older patients as well. Remission was achieved in approximately one fifth of the patients. This number is in line with remission achievements in other observational studies. The German registry, RABBIT, showed a remission rate achieved in 16% of the patients under biological therapy[20]. In the Italian registry, MonitorNet, 36% of the patients were reported to be in remission[21]. The data from the German registry are from a publication from 2006, which can justify a lower value. The data from the Italian registry are from 2009 and only included patients who were started on biological therapy after 2007, which can partially explain the higher achievement of remission. Interpreting our findings in light of these other publications, we can conclude that our patients' disease activity control was in line with other observational studies and potentially with some room for improvement in this aspect. To our knowledge, no previous studies focused on the same aspect as we did, meaning that no studies specifically addressed the circumstances in which

Table IV. Comparison of the disease activity between older and recent switches

	n (%)	Subcohort 1§ (n = 56)	Subcohort 2¶ (n = 56)	Subcohort 3¤ (n = 67)	p value subcohort 3 *vs* subcohort 1
Disease activity control evaluable at last observation*	111 (90%)	56 (100%)	51 (91%)	60 (90%)	–
EULAR response evaluable	99 (89%)	43 (77%)	41 (80%)	56 (84%)	–
• Good	35 (35%)	8 (19%)	18 (42%)	17 (30%)	
• Moderate	52 (53%)	25 (58%)	20 (46%)	32 (57%)	0.23
• None	12 (12%)	10 (23%)	5 (12%)	7 (13%)	
Remission	24 (22%)	8 (14%)	11 (22%)	13 (22%)	0.30

§Subcohort 1: start of first biologic before 2007, follow-up period before 2007. For this cohort, the last observation is the first observation in the next follow-up period (beginning of 2007)
¶Subcohort 2: start of first biologic before 2007, follow-up period after 2007
¤Subcohort 3: start of first biologic after 2007, follow-up period after 2007
*By disease activity control evaluable at last observation is meant that the patient did not start a new biologic at the last evaluation, was not proposed to switch at the last evaluation and did not discontinue a biologic definitely, as these cases compromise the evaluation of disease activity control

switches take place or compared switches from earlier years with switches from more recent years.

The main limitation of the present study is the relatively small population. Some of the differences between the groups did not reach statistical significance and only remained as a trend. A second potential limitation is that not all patients that started biological therapy were included in the dataset, and therefore selection bias may have occurred. Nevertheless, all the efforts were done to include the maximum number of patients possible and we are confident that they are a good representation of the total population.

We strongly believe that this type of analyses provides clinicians with insight to their behavior in clinical practice. Clinicians might have the slightly deviated perception they are being interventive enough in their medical decisions, for instance of keeping or changing a therapy, and only when the reality is put into numbers can the misperceptions be understood. A parallelism can probably be established with situations when a tight control of RA is compared to routine clinical care, just as for example was illustrated in the TICORA trial, where it was demonstrated that a tight control led to significantly better outcomes[22]. This parallelism can at the moment only remain as an image to better illustrate the idea and, if deemed to be true, then a scientific demonstration will be required.

Conclusion

In summary, this study demonstrated that switches in biological therapy were more frequently performed in more recent years, compared to the period before 2007. Patients with switches in biological therapy performed in more recent years were older and had a shorter duration of biological therapy compared to switches in biological therapy before 2007. A trend could be shown towards a better and more targeted control of the disease. Nevertheless, there is still room for improvement, especially when aiming at remission and following the current EULAR recommendations for the treatment of RA[2], for example, applying a tighter therapy strategy, like the "treat to target model"[1].

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