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Porque Suspendemos os Agentes Biológicos? Estudo Retrospectivo de 11 Anos

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RESUMO – **Introdução**: Os agentes biológicos assumiram uma relevância crescente no âmbito da Dermatologia. Contudo, os eventos adversos (EA) associados a estes tratamentos e as razões para a sua suspensão não estão totalmente esclarecidos. O Objectivo deste estudo é analisar os motivos que conduziram à suspensão de terapêuticas biológicas e caracterizar o perfil de EA na população de doentes sob esta terapêutica. **Material e Métodos**: Estudo observacional descritivo dos doentes acima de 18 anos sob terapêutica biológica no Serviço de Dermatologia do Hospital de Santarém EPE, entre Janeiro/2007 e Dezembro/2017. Foram avaliadas as causas de suspensão terapêutica, definida como a omissão de pelo menos 2 administrações consecutivas do fármaco, independentemente do motivo implicado e da existência, ou não, de recomendação médica para tal. **Resultados**: Foram avaliados 262 ciclos de tratamento, correspondentes a 138 doentes. Psoríase foi o diagnóstico predominante (93,5% dos doentes). Foram avaliados ciclos de tratamento com 8 biológicos, tendo o etanercept (46,6%), o adalimumab (31,3%) e o ustecinumab (12,6%) sido os mais representados. No período em estudo registaram-se 167 suspensões, invocando-se 170 justificações. Os fundamentos mais frequentes para a suspensão dos biológicos foram: falência primária ou secundária (35,3%), EA (31,2%), factores relacionados com o doente/má adesão à terapêutica (17,1%), intervenção cirúrgica (7,1%) e excelente resposta clínica/ausência de lesões (6,5%). Nas suspensões terapêuticas motivadas por EA (n=53), as infecções foram a causa mais frequente (35,8%, n=19), seguidas de neoplasias (15,1%, n=8), alterações hematológicas (13,2%, n=7), sintomatologia neurológica (9,4%, n=5) e reacções no local da injecção (5,7%, n=3). **Conclusão**: A principal causa de suspensão de biológicos foi a falência terapêutica, logo seguida dos EA. Dois padrões distintos de suspensão dos biológicos foram aparentes: a descontinuação definitiva, geralmente decretada pelo médico por falência terapêutica primária ou secundária, e a suspensão temporária, frequentemente sem indicação médica formal, por EA, mais tarde retomando o mesmo agente biológico. Determinámos uma incidência superior de ciclos terapêuticos suspensos por EA do que o reportado na literatura. As suspensões temporárias por EA, frequentemente não valorizadas pelo dermatologista, são provavelmente sub-reconhecidas e contribuem para um padrão deficitário de utilização dos biológicos, com prejuízo dos resultados clínicos obtidos.

PALAVRAS-CHAVE – Suspensão do Tratamento; Terapia Biológica/efeitos adversos.

Why do we Discontinue Biologic Agents? A Retrospective Study of 11 Years

ABSTRACT – ***Introduction:*** *Biologic agents acquired a growing relevance in dermatology, however, adverse events (AE) and reasons to discontinue therapy are not completely known. The objective of this study is to analyse the reasons behind the discontinuation of biologics and characterize the AE in this population of patients.* ***Material and Methods:*** *Descriptive observational study, including patients over 18-years-old under treatment with biologic agents in the Dermatology Department of Hospital de Santarém, Portugal, between January/2007 and December/2017. We analysed reasons for therapeutic discontinuation, defined as the omission of at least 2 consecutive administrations, whatever the reason implicated and whether or not proposed by the dermatologist.* ***Results:*** *A total of 262 cycles of treatment were performed, in 138 patients (59.4% male, 40.6% female). Psoriasis was the most prevalent diagnosis (93.5% of the patients). Cycles of treatment with 8 biologic agents were analysed: etanercept*

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(46.6%), adalimumab (31.3%) and ustekinumab (12.6%) were the most represented. During the study period, 167 suspensions were registered, for which 170 justifications were indicated. The most prevalent causes were: primary or secondary therapeutic failure (35,3%), AE (31.2%), factors related to the patient/noncompliance (17.1%), surgical intervention (7.1%) and excellent clinical response/absence of lesions (6.5%). Among therapeutic discontinuations motivated by AE (n=53), infections were the most frequent cause (35.8%, n=19), followed by malignancies (15.1%, n=8), hematological abnormalities (13.2%, n=7), neurological symptoms (9.4%, n=5) and local reactions at the injection site (5.7%, n=3). ***Discussion:*** *The main cause for discontinuation of biologics was therapeutic failure, immediately followed by AE. Two different patterns of discontinuation were apparent: definitive suspension, commonly decided by the physician due to primary or secondary therapeutic failure, and temporary discontinuation, frequently without formal medical indication, due to AE, later resuming the same drug. We found a higher percentage of therapeutic cycles discontinued due to AE than reported in the literature. Temporary suspensions of the biologics due to AE, often not sufficiently valued by the dermatologist, are probably under-recognized and contribute to a suboptimal pattern of use of biologics and worse clinical outcomes*

KEYWORDS *– Biological Therapy /adverse effects; Withholding Treatment.*

INTRODUCTION

Biologic agents have acquired a growing relevance in dermatology. It is common to emphasize the increase in efficacy they provide to control multiple dermatoses. However, long-term safety profiles and associated adverse events (AE) are not completely known.[1] Clinical trials usually include highly selected populations, focus mainly on therapeutic efficacy, have limited follow-up periods and do not allow us to know entirely the safety profile of these drugs in real life. Although there are several recent publications on the real-world evidence showing that patients often have to discontinue treatment and/or switch biologic agents over time due to loss of effectiveness or AE,[2-6] literature has focused mostly on severe AE leading to definitive therapeutic discontinuation and therapeutic switches, or "drug survival", as a useful measure for evaluating the long-term treatment success of a biologic treatment in the real-world setting.[2,7,8]

All the causes that lead to definitive, or especially to transient therapeutic discontinuation, that we want to address in particular, are not so well-known and there is a scarcity of published data in the Portuguese population. Therefore, the objective of our study was to characterize discontinuation of biologic agents in a national dermatology department and analyze the underlying reasons, as well as the AE, evaluating both discontinuations decided by the physician and those without medical advice. Evaluation of drug survival was not, however, our primary outcome.

METHODS

A descriptive observational study was performed, including patients over 18-years-old under biologic treatment in the Dermatology Department of Hospital de Santarém, Portugal, between January/2007 and December/2017. Epidemiological and clinical data were reviewed from data on file and missing information was gathered via direct contact with the patient. The concept of "therapeutic discontinuation" was defined as the omission of at least 2 consecutive administrations of the biologic agent, in line with the concept used by Belinchón *et al*,[9] whatever the reason, whether or not ordered by a dermatologist and whether or not the patient later resumed the same biologic, switched to another one or was started on another therapeutic modality. The length of time the patient was continuously taking the biologic agent, not skipping more than one administration, was defined as a "cycle of treatment". No distinction could be performed between naive and bio-experienced patients. The AE included in the analysis were occurrences registered in the clinical records as causes of discontinuation, with a presumed relationship with the biologic agent, but the degree of severity could not be evaluated.

For the data analysis, binary and categorical variables were summarized by counts and percentages, and continuous variables by means. For each one of the most represented biologics, analysis was performed comparing number of discontinuations and percentage due to AE, period until the first discontinuation due to AE, differences in the number/percentage of discontinuations caused by each major AE and length of treatment until discontinuation for each of them. Comparison of means was performed using the independent samples t-test and ANOVA. Statistical analysis was performed using the IBM SPSS Statistics 23.0 (SPSS, Chicago, IL, USA). The level of significance was considered for $p<0.05$.

RESULTS

During the period of 11 years under analysis, biologic agents were prescribed to 138 patients, 82 males (59.4%) and 56 females (40.6%), both naive and biologic-experienced patients. Detailed epidemiological and clinical data are displayed on Table 1. Psoriasis was the predominant diagnosis (129/138), followed by hidradenitis suppurativa (4/138), pyoderma gangrenosum (2/138), dissecting cellulitis of the scalp (1/138), SAPHO (synovitis, acne, pustulosis, hyperostosis and osteitis) syndrome (1/138) and PASH (pyoderma gangrenosum, acne and hidradenitis suppurativa) syndrome (1/138).

A total of 262 cycles of treatment were performed and 8 different biologic agents were used during this period, with etanercept, adalimumab and ustekinumab representing, respectively, 46.6%, 31.3% and 12.6% of the total cycles of therapy (Fig. 1). On average, patients were treated with 1.4 biologic agents and performed 1.9 cycles of treatment. One hundred patients (72.5%) were treated with one single biologic drug during the period under analysis but 27.5% of the

Table 1 - Epidemiological and clinical data of the patients treated with each biologic, namely number of patients that used each drug, their sex distribution, average age at the onset of treatment, time since diagnosis, use of concomitant systemic therapies and comorbidities (diabetes mellitus, hypertension and dyslipidemia).

	Patients Treated (n)	Sex distribution M/F	Age at onset of treatment	Time since diagnosis (years)	Concomitant systemic therapy (%)	Diabetes Mellitus (%)	Arterial hypertension (%)	Dyslipidemia (%)
Etanercept	86	52/34	50.0	16.3	29.1	17.4	38.4	37.2
Adalimumab	58	38/20	49.2	17.5	37.9	22.4	48.3	44.8
Ustekinumab	30	17/13	48.2	20.0	23.3	16.7	30.0	23.3
Infliximab	12	4/8	46.0	17.5	41.7	0.0	33.3	8.3
Secukinumab	3	1 /2	40.0	26.0	33.3	0.0	0.0	0.0
Ixekizumab	1	1/0	57.0	32.0	100.0	0.0	0.0	0.0
Efalizumab	3	2/1	38.7	14.0	0.0	33.3	66.7	66.7
Golimumab	1	0/1	52.0	13.0	100.0	0.0	100.0	100.0
Total	194*	115/79*						

*38 patients were treated with more than one biologic agent (range 2-6)

patients were prescribed more than 1 agent (range 2-6 drugs; 2 drugs: 18.9%; 3 drugs: 6.5%; 4 drugs: 0.7%; 5 drugs: 0.7%; 6 drugs: 0.7%). At the end of the study period neither secukinumab nor ixekizumab had treatment periods that were long enough to measure adherence at 12 and 24 months.

During these 11 years, 167 discontinuations of treatment with biologic agents occurred, for which 170 justifications were indicated (in 3 cases there were 2 reasons invocated to discontinue treatment). Infliximab and etanercept presented the highest percentages of patients missing at least 2 consecutive administrations, both during the first 12 and 24 months of therapy, and ustekinumab showed the longest average time of treatment until the first discontinuation for any reason and, specifically, due to AE (Table 2). Ixekizumab had no discontinuations during the period in analysis.

Justifications to discontinue the biologics were primary or secondary therapeutic failure (n=60, 35.3%), AE (n=53, 31.2%), factors related to the patient/noncompliance to

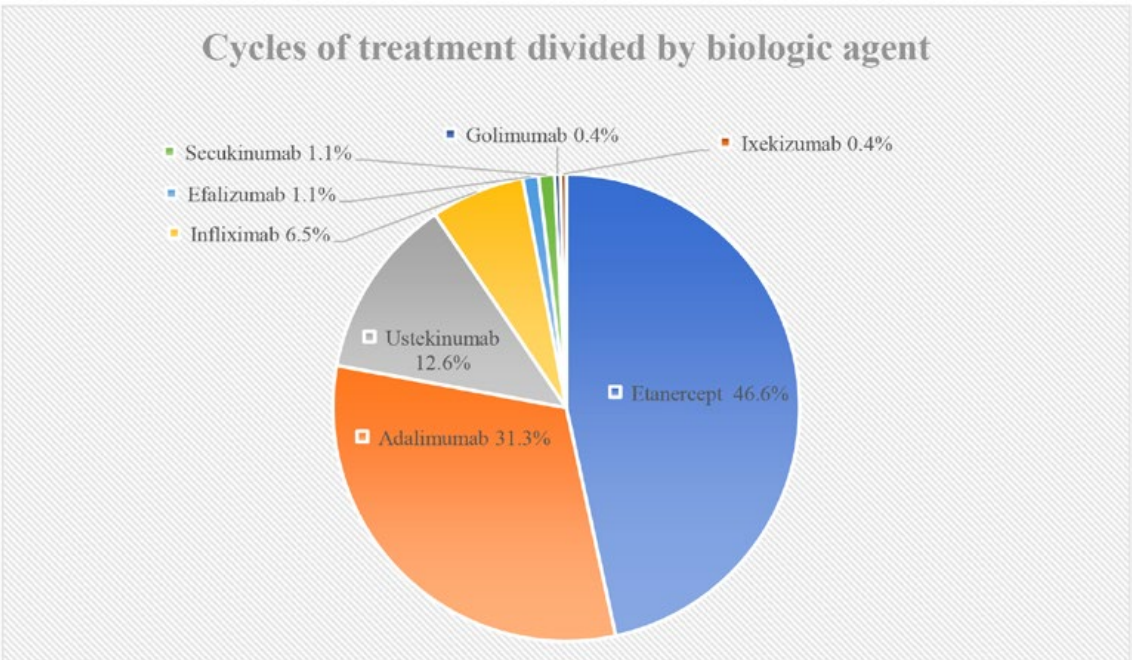

Figure 1 - Distribution of the cycles of treatment by biologic agent (n=262).

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Table 2 - Number of cycles of treatment for each biologic agent, respective number of discontinuations, time to the first discontinuation in all cases and when due to an AE and percentage of continuous therapeutic adherence/persistence at 12 and 24 months.

	Treatment cycles (n)	Number of discontinuations (n)	Time to 1st discontinuation (months)	Time to 1st AE discontinuation (months)	Continuous adherence at 12/24 months(%)
Etanercept	122	75	21.1	25.2	72.1/50.0%
Adalimumab	82	56	23.1	19.6	82.6/62.1%
Ustekinumab	33	16	25.9	28.4	83.3/60.0%
Infliximab	17	15	19.1	13.3	66.7/58.3%
Secukinumab	3	1	5.0	-	-/-
Ixekizumab	1	-	-	-	-/-
Efalizumab	3	3	7.3	-	0/0%
Golimumab	1	1	48.0	48.0	100/100%
Total	262	167			

the treatment (n=29, 17.1%), surgical intervention (n=12, 7.1%), excellent clinical response/absence of lesions (n=11, 6.5%), pregnancy (n=3, 1.8%) and other causes (n=2, 1.2%) (Table 3).

For the most represented agents, therapeutic failure motivated discontinuation of 29.4% of cycles for infliximab, 25.6% for adalimumab, 22.1% for etanercept and 12.1% for ustecinumab. In the case of suspension due to therapeutic failure (n=60), it was advised by the physician in 96.7% (n=58) of the cases, with switch to another biologic agent in 93.3% (n=56).

AE was the cause of therapeutic discontinuation of 20.2% (n=53) of the total 262 cycles of treatment, 26.2% for etanercept, 17.6% for infliximab, 15.2% for ustekinumab and 14.6% for adalimumab. Among AE, infections, mostly respiratory infections, were the most frequent cause of therapeutic discontinuation (n=19, 35.8%), followed by malignancies (n=8, 15.1%), hematological abnormalities (n=7, 13.2%), neurological symptoms (n=5, 9.4%) and local reactions at the injection site (n=3, 5.7%). There were 8 different cases of malignancy diagnosed, with no discernible predominant pattern: cutaneous melanoma, prostatic adenocarcinoma, endocervical adenocarcinoma, glioma, pelvic sarcoma, breast adenocarcinoma, penile squamous cell carcinoma and ampulla of Vater carcinoma. Hematological abnormalities were mainly cytopenias, particularly thrombocytopenia. On average, for patients who discontinued due to AE, treatment was performed for 24.0 months until the first suspension. Regarding discontinuations due to AE (n=53), they were unilaterally decided by the patient in 35 cases (66.0%) and advised by the physician in 18 (34.0%). After discontinuation, the same medication was reintroduced in 30 cases

Table 3 - Causes of therapeutic discontinuation for each drug and the number and % of discontinuation per number of cycles.

Causes of discontinuations	Etanercept N=75	Adalimumab n=56	Infliximab n=15	Ustekinumab n=16	Secukinumab n=1	Efalizumab n=3	Golimumab n=1
Therapeutic failure	27 (22.1%)	21 (25.6%)	5 (29.4%)	4 (12.1%)	1 (33.3%)	2 (66.7%)	-
AE	32 (26.2%)	12 (14.6%)	3 (17.6%)	5 (15.2%)	-	-	1 (100.0%)
Factors related to the patient	10 (8.2%)	12 (14.6%)	2 (11.8%)	4 (12.1%)	-	1 (33.3%)	-
Surgical intervention	4 (3.3%)	5 (6.1%)	2 (11.8%)	1 (3.0%)	-	-	-
Excellent clinical response	3 (2.5%)	4 (4.9%)	2 (11.8%)	2 (6.1%)	-	-	-
Pregnancy	2 (1.6%)	-	1 (5.9%)	-	-	-	-
Other causes	-	2 (2.4%)	-	-	-	-	-
Total	78*	56	15	16	1	3	1

* in 3 cases there were 2 causes for drug discontinuation

(56.6%), in 6 cases (11.3%) there was a switch to a different biologic agent and in the remaining 17 cases (32.1%) other therapeutic modalities were started.

Although differences were found between the four major biologic agents prescribed (etanercept, infliximab, ustekinumab and adalimumab), they did not reach statistical significance in the following aspects: number of discontinuations (t = 2.660, sig. 0.077) and percentage due to AE (t = 1.964, sig. 0.144), period until the first discontinuation due to AE (F 0.329; sig. 0.804), differences in the number/percentage of discontinuations caused by each of the major AE (infections: t = 1.608, sig.0.206; neoplasms: t = 1.852, sig.0.161; hematological abnormalities: t = 2.333, sig. 0.102) and length of treatment until discontinuation (sig>0.05).

DISCUSSION

Therapeutic adhesion to biologic agents can be poor, with high rates of discontinuation and modification of treatments.[10,11] The main cause of discontinuation of biologic agents in the literature is primary or secondary therapeutic failure,[2,7,12] a finding corroborated by our experience.

Etanercept and infliximab showed the highest levels of discontinuation caused by AE, whereas ustekinumab showed the longest mean period of treatment until discontinuation due to AE, similar to previous studies.[2,11-13] Infections and neoplasms were the commonest AE, causing discontinuation of 10.4% of the total number of therapeutic cycles.

We found a higher percentage of therapeutic cycles discontinued due to AE (20.2%) than generally described in the literature,[2,11,12] attributable to differences in methodology. We defined therapeutic discontinuation by a tight criterion, as the omission of 2 consecutive administrations of the drug, independent on the normal treatment intervals (1, 2, 4 or 12 weeks), whether the patient was later initiated on another treatment or maintained on the previous, so that data could reflect, not only definitive suspensions followed by a switch of the drug, but also transient discontinuations soon resuming the same biologic agent.

Analyzing the context in which therapeutic discontinuation occurred, two clearly different patterns emerged. Discontinuations due to primary or secondary therapeutic failure were almost invariably advised by the physician (96.7%), and were followed by switching to another biologic in 93.3% of cases. Suspensions due to AE were more commonly on patient's own initiative, without medical advice, were transient in the majority of cases (56.6% resumed the same biologic), and only 11.3% of the patients switched the biologic agent. AEs were a relatively rare cause of definitive therapeutic discontinuation and switch, probably because we also considered minor AE that led to temporary discontinuation decided by the patient.

Our higher figures compared to other published reports reflect this subgroup of temporary discontinuations caused by AE, not severe enough to justify a definitive discontinuation and therapeutic change, and frequently underestimated. And there is evidence that even transient discontinuations may have consequences on the efficacy of the biologic agent, associating with worse long-term outcomes when compared with continuous treatment.[14]

Limitations of the study

Our study presents data obtained from a large sample in the real world practice. There are, however, several limitations. All the 8 different drugs, that have different mechanisms of action, different dosages and treatment protocols were evaluated in a global way, without considering the indication that motivated their use. Moreover, data were retrospectively collected, mostly from clinical records produced by different physicians, with the inherent subjectivity and biases in evaluations of efficacy, therapeutic failure as well as AE. Further data regarding the characterization of the population, including scores of disease severity, were not included due to an irregular use of standardized measures or scores in the period in analysis. Differences between patients naive to biologic therapy and biologic-experienced patients were not studied. Moreover, we defined treatment discontinuation, the main objective of our study, as the interruption of 2 successive doses, regardless of its cause and posterior therapeutic decisions, which may have a different impact for therapies programmed for intervals of 1 week or 12 weeks.

CONCLUSION

We can conclude that therapeutic discontinuations during biologic therapy occurred under different scenarios, including non-medical oriented suspensions or often-neglected transient discontinuations. A mere analysis of switches of biologic agents would not give us the right perspective of therapeutic discontinuations, as many patients who temporarily discontinue treatment, even due to an AE, later resume the same biologic.

Temporary discontinuations of biologic agents due to transient AE or other causes, often decided by the patient without medical indication, and not sufficiently valued by the dermatologist, are probably under-recognized and can contribute to a suboptimal pattern of use of these drugs and may have an impact on clinical outcomes.

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