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Relationship between injection site reactions and different adalimumab formulations. Analysis of the adverse events reported in Italy in 2016-2019

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Abstract. – OBJECTIVE: The adalimumab originator Humira® introduced a new citrate-free formulation in 2016, before the patent expiry that occurred in the European Union in October 2018. Some of the adalimumab biosimilars that were subsequently marketed are citrate-free, while others are not. Since citrate as an excipient is associated with pain at the injection site, recent anecdotical reporting in Italy raised the issue of possible prescription biases related to the differences in formulation existing among the various adalimumab products.

In this study, we analyzed the data obtained from the 'Rete Nazionale di Farmacovigilanza' (Pharmacovigilance National Network) to investigate whether, and to what extent, the differences in the formulation of the various adalimumab versions had an impact on the rate of injection site reactions reported in Italy in the period 2016-2019.

MATERIALS AND METHODS: A search was conducted based on 3 search criteria: (1) time frame; (2) suspected drugs, and (3) adverse reaction type. Reports classified in the System Organ Class "Administration site conditions" were analyzed by year, product, and type of adverse event (whether including or not 'pain'). Data were reported both as absolute numbers, as well as signaling rates, considering the consumption data expressed as defined daily doses (DDD).

RESULTS: We found that: (1) The change in Humira® formulation introduced in august 2016 was followed by a decrease in the reports of injection site reactions (from 45 in 2016 to 12, 12 and 8 in 2017, 2018, and 2019, respectively); (2) after the introduction of biosimilars during 2018, in 2019 a marked shift in reporting toward biosimilars was observed (52 out of 60; 87%).

CONCLUSIONS: While the decrease in Humira® reports is consistent with the improved tolerability of the new formulation, the huge increase in biosimilar reporting may be only in part explained by the differences in formulation and cannot be accounted for by a parallel increase in exposure, since 58.3% of total DDDs provided in 2019 were still attributed to Humira®.

Key Words:
Adalimumab, Biosimilars, Pharmacovigilance, Adverse reactions, Excipients.

Introduction

The originator of the anti-TNF monoclonal antibody (mAb) adalimumab, Humira® was issued a marketing authorization valid throughout the European Union (EU) on September 8, 2003[1]. Humira® patent definitely expired on October 16, 2018 (after the exploitation of a supplementary protection certificate)[2], raising the possibility to launch on the EU market adalimumab biosimilars, which had already obtained a marketing authorization (MA) in EU before Humira® patent expiry; these included Amgevita®, Hyrimoz®, and Imraldi®.

The original Humira® formulation included: (1) a phosphate/citrate buffering system, sodium chloride, mannitol, polysorbate 80, and water for injection as excipients; (2) 40 mg of the active ingredient in a 0.8-ml injection volume; (3) prefilled syringes with 27-gauge needles[3]. Before patent expiry, the MA holder of Humira Abbvie introduced a new formulation including: (1) citrate-free excipients; (2) a reduced 0.4-ml injection volume, and (3) 29-gauge syringe needles, aiming to decrease the rate of injection site reactions, which were previously reported in 12.9% of

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patients receiving Humira®[3]. The new citrate-free Humira® formulation was released on the Italian market on August 17, 2016[4]. It is worthy of note that some of the biosimilars marketed later have citrate among the excipients (Hyrimoz®, Idacio®, and Imraldi®) whereas others (Amgevita® and Hulio®) are citrate-free[3].

While changes in formulation improving tolerability and patient adherence to the treatment are generally thought to be useful and worth doing, recent anecdotal reporting raised the issue of possible prescription biases related to the differences in formulation existing among the various adalimumab products available in Italy. To address this issue, we carried out a search on the national database of adverse drug reaction '*Rete Nazionale di Farmacovigilanza*' (RNF, Pharmacovigilance National Network) to investigate whether, and to what extent, the differences in formulation existing among the various adalimumab versions had had an impact on the rate of injection site reactions reported in the period 2016-2019.

Materials and Methods

A search was conducted in the RNF based on 3 search criteria:

1) **Time frame.** The data entry in the RNF had to be included between Jan 1, 2016 and Dec 31, 2019;
2) **Suspected drugs.** All reports including adalimumab among the suspected drugs: the originator Humira® (Abbvie Deutschland GMBH & CO.KG) and its biosimilars Amgevita® (Amgen Europe B.V.), Hyrimoz® (Sandoz GMBH), and Imraldi® (Samsung Bioepis NL B). Hulio® (Mylan S.A.S.) and Idacio® (Fresenius Kabi Deutschland GMBH) were also approved in Italy before December 2019, but they were not on the market; therefore, no report was associated with these two products;
3) **ADR type.** Reports within the System Organ Class (SOC) "General disorders and administration site conditions".

Literature reports were not included in the search.

On the set of data obtained from the above search, a further selection was carried out, including only 'Administration site conditions', yielding a sub-group of data focusing on the primary objective of the study. This subset of data was further analyzed by years and by drug.

Among the administration site conditions, certain AEs can be specifically related to the presence of sodium citrate in the formulation, i.e., pain and/or burning at the site of injection, whereas other AEs have a weaker patho-physiological relationship with the excipient citrate, e.g., pruritus, erythema, swelling, etc. Based on this reasoning, we introduced a classification in type-I and type-II reactions, with type-I including all reports specifically mentioning terms related to 'pain' and/or 'burning' at the site of injection (along with other possible AEs), whereas type-II reactions included the remainders. Type-I and type-II reactions were also analyzed by years and by drug.

Data were expressed both as absolute numbers, as well as signaling rates, i.e., the number of AEs/100.000 DDDs/year, considering the consumption data of each product in the time-frame 2016-2019. Descriptive statistics were used to report the data; no inferential testing was carried out.

Results

The search carried out in the RNF yielded 1264 reports for selected suspected drugs. As expected, none of these reports was referring to the products Hulio® and Idacio®. The subsequent selection per 'Administration site condition' resulted in a subgroup of 171 reports, which were then divided in type-I and type-II reactions according to the classification criteria defined in 'Materials and Methods'. Type-I and type-II reactions were 62 and 109, respectively (Figure 1). In most cases, the reports included more than one adverse event belonging to the same SOC. Type-I reactions included 'Pain' and/or 'Burning', along with many others; in total, 84 AEs were reported (Table I). Likewise, type-II reactions included a large collection of different AEs, to a total of 149 (Table I). The further analysis by year and by medicinal product caused 29 reports (8 type-I and 21 type-II) had to be excluded by the final analysis because the date of reaction and/or the drug's brand name were missing. Thus, the final analysis included 54 type-I and 88 type-II reactions (Figure 1).

Table II shows the time-course of type-I and type-II reactions attributed to the four adalimumab versions in the time-frame 2016-2019. Considering the total number of reactions per each product, Humira® had 45 reports in 2016, this

Table I. Adverse drug reactions described by number of reports and by Preferred Term. The ADRs were divided into type-I and type-II reactions according to the criteria described in the 'Materials and Methods' section.

Type I local reactions	No.	Type II local reactions	No.
Injection site pain	30	Injection site rash	22
Injection site burning	22	Injection site pruritus	22
Injection site pruritus	5	Injection site reaction	21
Administration site pain	5	Injection site erythema	13
Injection site swelling	3	Injection site swelling	12
Injection site rash	3	Injection site tumefaction	7
Administration site burning	2	Infusion site tumefaction	7
Injection site edema	1	Injection site edema	6
Injection site reaction	1	Injection site hematoma	4
Injection site bruise	1	Infusion site pruritus	4
Injection site erythema	1	Injection site skin eruption	3
Injection site tenderness	1	Injection site urticaria	3
Injection site numbness	1	Injection site inflammation	2
Injection site discomfort	1	Injection site eczema	2
Injection site bleeding	1	Injection site vesicles	2
Pain during injection	1	Application site rash	2
Administration site edema	1	Injection site infiltration	1
Administration site pruritus	1	Injection site irritation	1
Infusion site burning	1	Injection site induration	1
Infusion site erythema	1	Injection site lesion	1
Post-procedure tumefaction	1	Injection site ecchymosis	1
		Injection site deformation	1
		Injection site discoloration	1
		Injection site bulge	1
		Administration site reaction	1
		Administration site pruritus	1
		Administration site eruption	1
		Administration site paresthesia	1
		Infusion site rash	1
		Application site pruritus	1
		Application site erythema	1
		Local tumefaction	1
		Local reaction	1
	84		149

figure dropping to 12 reports in 2017 and 2018, and 8 reports in 2019. The first reports referring to biosimilars appeared in 2018, with 6 AEs attributed to Imraldi® and 1 to Amgevita®. In 2019, the large majority of AEs (52/60) were attributed to biosimilars, with 30 reports for Imraldi®, 17 reports for Amgevita®, and 5 reports for Hyrimoz®.

Table III shows the total number of reactions per each drug, along with their respective consumption data expressed as DDDs. The signaling rates, expressed as the number of reactions/100.000 DDDs/year, is also shown. Interestingly, Humira® had 68.2% of all ADRs reported in 2018, in front of 98% of all DDDs utilized, whereas Imraldi® had 27.3% of all ADRs reported, in front of 1% of the DDDs utilized. In 2019, the percentage of ADRs attributed to Humira® dropped to 13.3%, in front of 58.3% of all DDDs utilized; conversely, Imraldi® had 50% of ADRs attributed, in front of 12.5% of DDDs. Amgevita® had 4.5% of all ADRs reported in 2018, in front of 1% of all DDDs utilized, and 28.3% of all ADRs reported in 2019, in front of 26.3% of all DDDs utilized. Hyrimoz® had only reports in 2019, with 8.3% of all ADRs reported, in front of 2.8% of all DDDs utilized.

Discussion

Data from the RNF concerning the administration site reactions attributed to adalimumab in the period 2016-2019 show that: *i*) after an initial figure of 45 in 2016, reports concerning Humira® had a marked decrease from 2017 onward, with 12 reports in 2017 and 2018, and 8 reports in 2019; *ii*) after their launch on the market in 2018, adalimumab biosimilars (namely Amgevita®, Hyrimoz®, and Imraldi®) taken collectively had a majority of reports in 2019 (52/60, 87%).

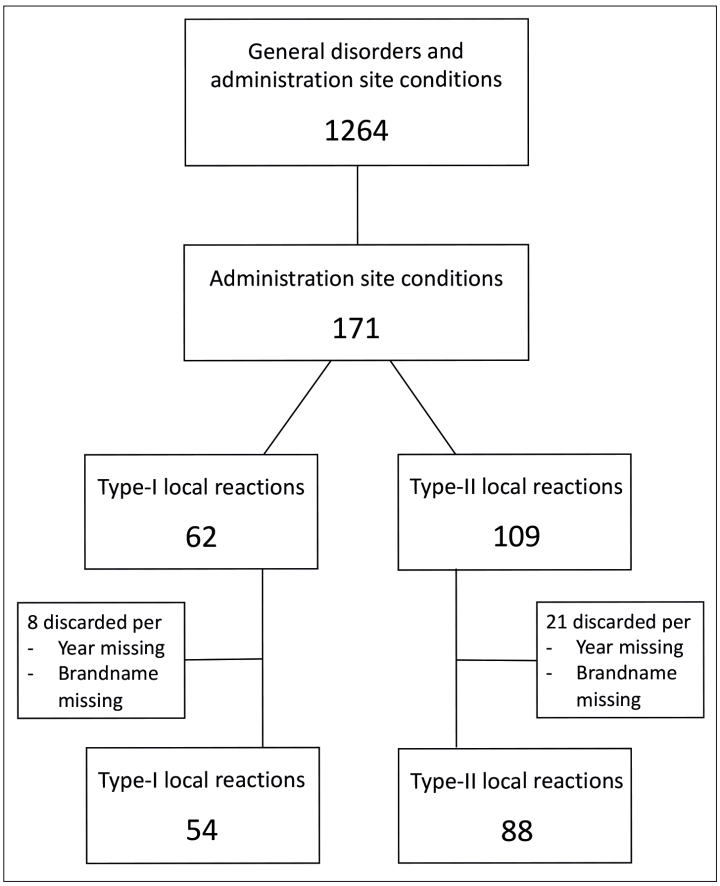

Figure 1. Flow chart of search and selection. Type-I and type-II AEs are defined in 'Materials and Methods'.

How to interpret these findings? As far as Humira® is concerned, a relationship could exist between the introduction of new citrate-free formulations in August 2016 and the decrease in reports of injection site reactions observed thereafter. The MAH Abbvie had previously demonstrated a difference in tolerability between the original formulation and the new 0.4-ml citrate-free formulation in 2 sibling Phase II, randomized, single-blind, two-period crossover clinical trials on a total of 125 patients with rheumatoid arthritis. The patients were either naive to anti-TNF or under treatment with the 40 mg/0.8 ml formulation; they were randomized to receive 40 mg/0.8 ml or 40 mg/0.4 ml Humira® at visit 1. After 1 or 2 weeks, patients received the other formulation at visit 2. The primary endpoint was pain after injection, assessed through a pain VAS [McGill Pain Questionnaire (MPQ-SF)] and the Draize scale evaluated immediately after injection and 15 min post-injection. The mean difference on the VAS for the pooled data (-2.48 cm) was considered by the authors as clinically relevant, so were other endpoints assessing the tolerability and safety profile[5]. A higher pain perception associated with Humira® citrate

Table II. Adverse drug reactions reported per year (in the time-frame 2016-2019), adalimumab product, and type of reaction, whether it was type-I or type-II according to the criteria described in the 'Materials and Methods' section.

	2016			2017			2018			2019		
	Type-I	Type-II	Total	Type-I	Type-II	Total	Type-I	Type-II	Total	Type-I	Type-II	Total
Amgevita	-	-	-	-	-	-	-	1	1	5	12	17
Humira	16	29	45	3	12	15	3	12	15	-	8	8
Hyrimoz	-	-	-	-	-	-	-	-	-	2	3	5
Imraldi	-	-	-	-	-	-	5	1	6	20	10	30
Total	16	29	45	3	12	15	8	14	22	27	33	60

Table III. Adverse drug reactions per each adalimumab product reported per year, along with their respective consumption data, expresses as defined daily doses (DDDs), and the signaling rates, expressed as the number of reactions per 100,000 DDDs per year.

	Adverse drug reactions				Defined Daily Doses				Signaling rate (x 100.000 DDDs)			
	2016	2017	2018	2019	2016	2017	2018	2019	2016	2017	2018	2019
Amgevita	-	-	1	17	-	-	195,960	5,566,679	-	-	5.1	3.1
Humira	45	15	15	8	15,893,288	17,057,969	18,226,735	12,343,437	2.8	0.9	0.8	0.6
Hyrimoz	-	-	-	5	-	-	-	599,007	-	-	-	8.3
Imraldi	-	-	6	30	-	-	180,935	2,648,143	-	-	33.2	11.3
Total	45	15	22	60	15,893,288	17,057,969	18,603,629	21,157,266	2.8	0.9	1.2	2.8

formulation was reported by Gely et al[6], who also showed that pain perception was markedly reduced after switching to the new citrate-free formulation. Rosembert et al[7] reported that patients switching from originator adalimumab to biosimilar adalimumab were more likely to report injection-site problems if the biosimilar was buffered with citrate versus citrate-free buffer. In contrast, a recent report from the UK National Health Service (NHS) based on 6 months' usage of adalimumab biosimilars in 35,000 patients reported injection-site discomfort across products regardless of citrate content[8].

Taken together, the present findings and the data from literature indicate that the decrease in reports of AEs related to injection site reactions to Humira® administration is associated with improved tolerability of the new citrate-free formulation. Consistently, the Humira® signaling rate steadily decreased from 2.8 in 2016 (when the citrate formulation was still on the market) to 0.9, 0.8, and 0.6 in 2017, 2018, and 2019, respectively. Thus, a 2.8 rate of signaling might be taken as a paradigm of the expected rate of signaling for adalimumab formulations including citrate. With this in mind, we observed that the rates of signaling for adalimumab biosimilar on average were higher, regardless of whether the biosimilar formulations were citrate-free (5.1 and 3.1 for Amgevita® in 2018 and 2019, respectively) or not (33.2 and 11.3 for Imraldi® in 2018 and 2019, respectively; 8.3 for Hyrimoz® in 2019). It is reasonable to think that other factors, apart from local tolerability of biosimilar formulations, may have induced such apparent over-reporting. For example, we noticed that 22 out of 36 reports concerning Imraldi®, i.e., about 60%, come from a single Region, Tuscany, where a decision by the local government (n. 194; Feb 26, 2018) established that only products acquired by tender should be used in the Region, and subsequently Imraldi® was awarded the tender. A local Tuscany guideline states that "both naive patients and patients under treatment with the originator will receive the biosimilar awarded the public tender, unless the prescriber indicates a motivated different choice"[9]. Thus, it is conceivable that in Tuscany the reports of injection site reactions with Imraldi® (the RNF also recorded a number of failure reports) may have served prescriber's will to use alternative adalimumab products.

Conclusions

The changes in Humira® formulation introduced in 2016 were aimed at improving tolerability and indeed were followed by a decrease in the reports of injection site reactions (from 45 in 2016 to 12, 12 and 8 in 2017, 2018, and 2019, respectively). While such decrease is consistent with the improved tolerability of the new formulation, the parallel, huge increase in biosimilar reporting may be only in part explained by the differences in formulation and cannot be accounted for by a parallel increase in exposure, since Humira® had still 58.3% of all DDDs utilized in 2019, in front of 13.3% of all ADRs, whereas biosimilars altogether had 86.6% of all ADRs with 41.7% of all DDDs.

Conflict of Interest

Daniela Pilunni, Carmela Santuccio, Laura Sottosanti, Patrizia Felicetti and Pierluigi Navarra declare no conflict of interest.

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Ethics Approval
Ethical approval was not required for this study.

Consent for Publication
Publication of the study has been approved by AIFA, Direzione Generale, Rome, Italy.

Availability of Data and Material
Data obtained from the 'Rete Nazionale di Farmacovigilanza' (Pharmacovigilance National Network, AIFA), Rome, Italy.

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