ORIGINAL ARTICLE

Post-marketing dosing changes in the label of biologicals

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AIM

The aim of this study was to evaluate post-marketing label changes in dosing information of biologicals.

METHODS

Biologicals authorized between 2007 and 2014 by the European Medicines Agency (EMA) were included and followed up from marketing authorization until 31 December 2016 or date of withdrawal of the marketing authorization. The primary outcome of the study was defined as label change in dosing information for the initially approved indication. Incidence of changes, type of change and mean time to change were assessed. As a secondary outcome, label changes in dosing information for extended indications were assessed.

RESULTS

A total of 71 biologicals were included. Dosing information in the label changed for the initial indication during follow-up for eight products (11%). In one of the eight products the change concerned an increase in dose. Also, a change in dosing frequency was identified in three products, for one product a recommendation was added that therapy could be initiated with or without a loading dose, and for one product the minimum dose was removed and a maximum dose was added. For the remaining product the dose was decreased due to safety issues. For 30 products (42%) the indication was extended at least once. No changes in dosing information were observed for the extended indications (n = 59) during follow-up.

CONCLUSIONS

This study showed that in 11% of the biologicals, the dosing for the initial indication in the label was changed. In contrast to small molecules, the dose was rarely reduced for safety reasons.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT
• Dose changes in the label occur frequently (~20%) in the post-marketing phase of new substances.
• Most often these dose changes are downward adjustments related to safety concerns.
• Limited information about dose changes is available for biologicals.

WHAT THIS STUDY ADDS
• In 11% of the biologicals the dosing information for the initial indication was changed in the post-marketing phase.
• For biologicals dose changes were rarely a reduction because of safety reasons.
• No changes in dosing information for extended indications were observed during follow-up.

Introduction

The drug dose aims to optimally balance efficacy, tolerability and safety when treating patients. The drug label, also called the Summary of Product Characteristics in the European Union, informs health care professionals as well as patients about the recommended dose for a given indication. The dose of a (biologic) drug in first-in-man studies is determined based on non-clinical data and subsequently further established in clinical studies. For biologicals, it is different and more difficult to predict their clinical effects from non-clinical data than it is for small molecules because of the complex protein nature of biologicals [1, 2]. Specifically, immune reactions such as hypersensitivity reactions and the formation of anti-drug antibodies are effects for which prediction by animal models is difficult [3]. Also, evidence generation from (non-)clinical trials can be limited by various factors such as the relatively small sample size, the homogeneity of the included population, and the lack of long-term follow-up. Studies conducted after marketing authorization of a new drug, including clinical trials, patient registries and large population-based database studies, aim to provide more information about the efficacy and safety. This post-marketing data can lead to changes in different sections of the label of the product, including the section on dosing information. Previous research showed that the dosing information in the label changed in the post-marketing setting for 21% of new active substances approved by the US Food and Drug Administration (FDA) between 1980 and 1999 [4]. In the majority (71%) of the label changes, the dose was reduced, implying that patients may initially be exposed to higher doses than acceptable or needed for the optimal treatment [4]. These FDA approval-based findings prompted the European Medicines Agency (EMA) to perform a study on EMA-approved new active substances which showed a comparable frequency in label changes [5]. In addition, it was shown that major issues regarding the dose were raised for 10% of the new active substances during the assessment of the marketing application [5].

Dose changes are most often implemented in order to optimize the risk–benefit balance. The ipilimumab example (Box 1) illustrates the difficulties that companies as well as regulators face when finding the dose with the optimal risk–benefit balance for biologicals. Besides increasing the total dose for efficacy-related reasons, the dose can also be increased to prolong the duration of the effect. Due to the pharmacokinetic properties of biologicals, the target can become saturated. In that case the duration of the effect is prolonged [6, 7].

Box 1

Example difficulties faced in dose tuning

Ipilimumab, a monoclonal antibody activating the immune system by targeting CTLA-4, was approved in the European Union in 2011 for the treatment of advanced melanoma [22]. The recommended dose for ipilimumab was 3 mg kg^{-1} every 3 weeks based on the pivotal phase three study. However, there were uncertainties whether the 3 mg kg^{-1} dose induces the maximum pharmacological effect as the pharmacodynamics marker of immune cell activation was increased for the 10 mg kg^{-1} dose compared to the 3 mg kg^{-1} dose. Also, a phase two study had indicated that the 10 mg kg^{-1} dose may be more efficacious though accompanied by an increased number of serious adverse events. As there were multiple differences between those two studies it was not possible to directly compare the results [22]. Based on this information it was concluded that it was not fully clear whether 3 mg kg^{-1} is the optimal dose for ipilimumab. Therefore, at approval the regulatory authorities decided that the company should commit to perform a study comparing the efficacy and safety of 3 mg kg^{-1} with 10 mg kg^{-1}. Results of this study became available in 2017 and confirmed that the 10 mg kg^{-1} dose resulted in a significant increase in overall survival compared to the 3 mg kg^{-1} dose, but also in more (serious) adverse events [23–25]. The results of this study were included in the label, however, not in the section on dosing information [23].

Dose changes can also be introduced as part of the extension of indication. The dosing information for a new therapeutic indication may then differ from the dosing information for the initial indication. For example, rituximab was initially indicated for non-Hodgkin's lymphoma at EU approval in 1998 with a recommended dose of 375 mg m^{-2} body surface area per cycle [8]. In 2009, the indication was extended to include another haematological cancer type, chronic lymphocytic leukaemia [8]. The recommended dose is 375 mg m^{-2} body surface area in the first cycle followed by 500 mg m^{-2} body surface area in the subsequent cycles. Also, the indication was extended to include a non-oncology indication, rheumatoid arthritis, with a

recommended dose of 1000 mg followed by a second 1000 mg 2 weeks later [8].

As described, difficulties are faced in establishing the optimal dose. However, little is known about changes in dosing information for biologicals during the post-marketing phase. Our study aimed to provide insight into the frequency and nature of post-marketing label changes in dosing for the initial indication of EMA-approved biologicals. Also, changes in the dosing information for the extended indications were assessed.

Methods

We included biologicals authorized between 1 January 2007 and 31 December 2014 via the centralized procedure of the EMA. According to EMA's definition, biologicals are products produced by or extracted from a biological source [9]. We defined biologicals more strictly as recombinant therapeutic (glyco) proteins, thus excluding vaccines, diagnostic proteins, and blood-derived products. Information on the approval circumstance (normal, conditional, under exceptional circumstances) and orphan designation (yes, no) of the biologicals was retrieved from the EMA website. Furthermore, biologicals were classified into the mechanistic classes of antibodies, cytokines, enzymes, growth factors, hormones, interferons, receptors and other/various [10]. The product assessment history was retrieved from the EMA website and was used to determine whether a label change in dosing information for the initial indication had

occurred and whether the indication was extended. If the assessment history did not provide sufficient information on the occurrence of a label change in dosing, the regulatory assessment report was consulted through the database of the Dutch Medicines Evaluation Board. The biologicals were followed up until 31 December 2016 or until the date of withdrawal if a product was taken off the market.

Incidence of dosing information changes in the drug label, type of dosing information change and time to the dosing information change in the drug label change were assessed. We defined a change in dosing information in the label for the initial indication as an increase or decrease in the dose per dose interval, including increase or decrease in the frequency of administration, the dose given per administration, or the duration of the treatment period, and other dose changes (e.g. change in dosing frequency without a change in total dose; 200 mg every 2 weeks changed to 400 mg every 4 weeks). First, the incidence of the occurrence of change in dosing was assessed by dividing the number of changes by the number of biologicals in the cohort. Relative risks, including 95% confidence interval for the occurrence of the first change in dosing for the different determinants, was measured using Cox regression. A Kaplan–Meier analysis was performed to analyse the time to a label change in dosing. If the dosing of a product had changed more than once, only the first change was taken into account for the Kaplan–Meier analysis. The data analysis was performed using SPSS for Windows, version 24.0.

In addition to the changes in dosing information of the initial indication, we determined whether the indication was extended during follow-up. When the indication was

Table 1

Biologicals whose dosing information was changed in the label for the initial indication

Biological	Disease category [26]	Description of the label change in dosing information	Time to change (years)
Abatacept	Diseases of the musculoskeletal system and connective tissue	Treatment may be initiated with or without the previously required intravenous loading dose.	6.9
Canakinumab	Diseases of the musculoskeletal system and connective tissue	Increase in the maximum dose from 300 mg or 4 mg kg^{-1} every 8 weeks to 600 mg or 8 mg kg^{-1} every 8 weeks.	3.3
Certolizumab	Diseases of the musculoskeletal system and connective tissue	Addition of an alternative dosing regimen (400 mg every 4 weeks) to the approved dosing regimen (200 mg every 2 weeks) for the treatment of patients with rheumatoid arthritis.	4.2
Corifollitropin alfa	Diseases of the genitourinary system	Increase in dose for patients >36 years and whose weight is between 50 and 60 kg from 100 μg to 150 μg.	4.8
Methoxy polyethylene glycol-epoetin beta	Diseases of the genitourinary system	Addition of an alternative dosing regimen (0.6 μg kg^{-1} once every 2 weeks) to the approved dosing regimen (1.2 μg kg^{-1} once a month) for patients who are not on dialysis and not currently treated with an erythropoiesis stimulating agent.	3.1
Ranibizumab	Diseases of the eye and adnexa	Change in dosing regimen, which is driven by monitoring of the stability of the disease. The initial dosing regimen was based on three initial monthly injections and re-treatment in case of loss of vision.	4.6
Romiplostim	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	Downward revision in cut-off value of thrombocyte count for the recommendation to decrease the dose and to interrupt the treatment.	1.8
Tocilizumab	Diseases of the musculoskeletal system and connective tissue	Removal of the recommendation for a minimum dose (480 mg) and addition of a maximum dose for patients >100 kg (800 mg).	1.4

extended, the dosing information of the extended indication was compared to the dosing information of the initial indication. The incidence of these differences, type of difference (increase, decrease, other) and time to first extension of indication were assessed. Furthermore, it was assessed whether the dosing information for the extended indications changed during follow-up by comparing the dosing information for the extended indication described in the label at time of the extension of indication to the dosing information in the label for the extended indication at end of follow-up. The labels were obtained from the publicly available community register of medicinal products of the European Commission.

Results

A total of 71 biologicals were included in this study (Appendix 1). Most of the biologicals ($n = 64$, 90%) were authorized under normal circumstances and did not have an orphan designation ($n = 58$, 82%). About a third ($n = 23$, 32%) of the biologicals were hormones, followed by antibodies ($n = 22$, 31%) and growth factors ($n = 10$, 14%). Within the follow-up time, a total of five biologicals (pegloticase, rilonacept, filgrastim ($n = 2$), eptotermin alfa), were withdrawn from the market, all for commercial reasons. Within the median follow-up time of six years (range: 2–10 years), the dosing information in the label for the initial indication was changed for eight products (cumulative incidence: 11%), as shown in Table 1 and Figure 1.

The time to the label change ranged from 1 to 7 years after marketing authorization with a median time to a change of 4 years (Figure 2).

For certolizumab and methoxy polyethylene glycol-epoetin beta, an alternative dosing regimen with the same total dose was added to the initial dosing regimen. For ranibizumab, the recommended dosing regimen was changed to a less restrictive regimen. For canakinumab and corifollitropin alfa, the dose was increased, whereas for abatacept and romiplostim, the dose was decreased. For romiplostim, the decrease in dose was related to safety. For tocilizumab, the minimum dose was removed and a
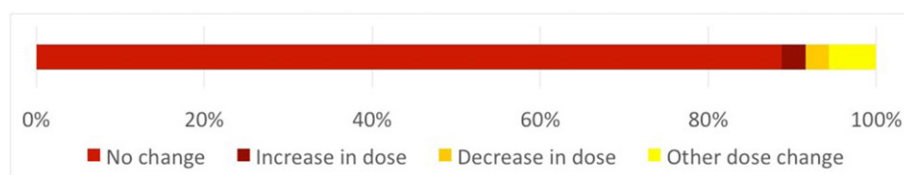

Figure 1

Nature and frequency of label changes in dosing information for the initial indication ($n = 71$)
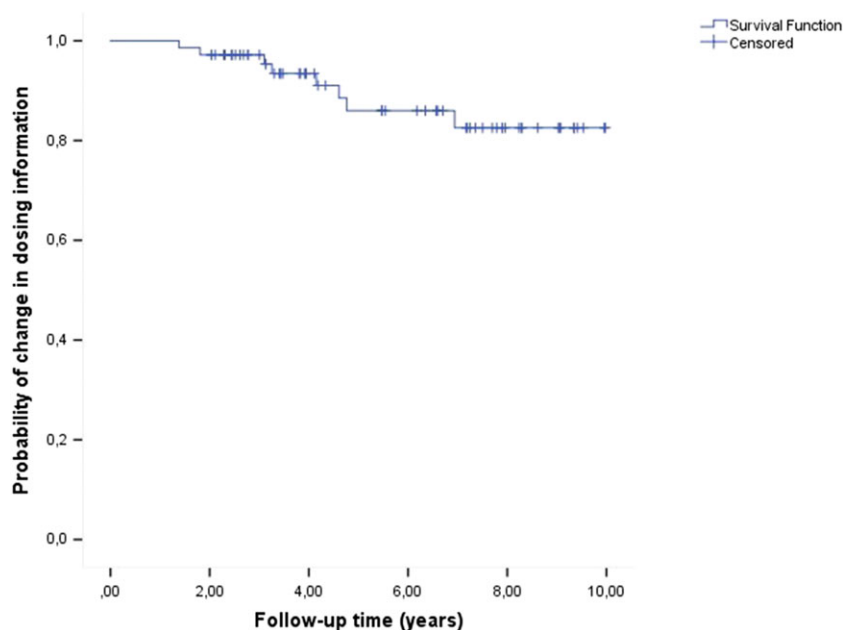

Figure 2

Kaplan–Meier curve for the change in the dosing information of the initial indication
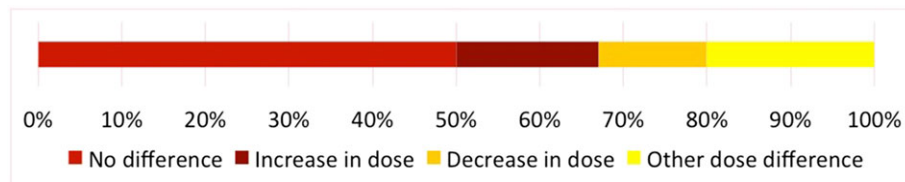
Figure 3

Nature and frequency of differences in dosing information in the label between the initial indication and the first extended indication (*n* = 30)

maximum dose was added. For three products within the cohort, more information about dosing became available after marketing authorization, but the outcomes of these studies did not warrant updates of the recommended dose in the label. We were unable to identify factors related to the label change in dosing information because the sample size was limited.

For 30 products (42%), the indication was extended at least once during follow-up with a median time to the first extension of three years (range: 1–7 years). The dose for the extended indication differed from the dose of the initial indication in 15 out of the 30 first extensions of indication (50%), as shown in Figure 3. For 14 products, the indication was extended more than once, resulting in a total of 59 extensions of indication. The dosing for the extended indication differed from the initial dosing in 32 out of these 59 extensions (54%). Furthermore, it was observed that for certolizumab and ranibizumab, the extension of indication was accompanied by a change in dosing information for the initial indication. During follow-up, the dosing information for the extended indications (*n* = 59) was not changed.

Discussion

For biologicals, more uncertainties exist about safety at the time of approval than for small molecules [11]. However, our study did not show that the dose of biologicals was reduced more often because of safety issues as compared to small molecules. Only one label change included a clear decrease in dose related to safety (romiplostim); the cut-off value warranting a decrease in dose was lowered to minimize the risk of thrombotic complications and was implemented following an international consensus report on the investigation and management of primary immune thrombocytopenia [12]. This is in contrast with the previous study on FDA-approved new active substances, which showed that the dose changes occurred more frequently and the dose change was mainly decreased in these products (71%) [4]. Four of the changes (abatacept, certolizumab, methoxy polyethylene glycol-epoetin beta, ranibizumab) observed in our study involved (additions of) alternative dosing regimens that reflected a less invasive approach for the patients' convenience [13–16]. The remaining three changes (canakinumab, corifollitropin alfa, tocilizumab) were considered efficacy-related changes implemented to optimize the risk–benefit balance. Comparable findings were shown in a study evaluating the rationale of dose selection for FDA-approved

biologicals in the pre-approval phase. This study showed that clinical efficacy attributed to the dose finding in 73% of the biologicals, whereas clinical safety attributed in 42% of the biologicals [17].

The extent to which dose changes occur may have been underestimated in our study as in clinical practice dose changes may be introduced based on experience from clinical practice. For example, in rheumatoid arthritis patients treated with TNF-alfa-inhibitors, the dose can effectively be down titrated [18], but down titration is currently not reflected in the label. Moreover, the recommended dose for rituximab in rheumatoid arthritis patients is 1000 mg followed by a second 1000 mg dose 2 weeks later. However, as of today, discussion is still ongoing whether this dose is the optimal dose and in clinical practice patients are often treated with 500 mg instead of 1000 mg [19, 20]. More recently, focus in clinical research has also shifted towards tapering of doses for medicines originally recommended for lifelong treatment, e.g. eculizumab, which may have beneficial economic effects [21].

Finally, the dose for the extended indication differed from the dose of the initial indication in half of the first extensions of indication. This indicates that research on dosing continues for extended indications, which may in the end also affect the dosing for the initial indication. In fact, we observed that for two products (certolizumab, ranibizumab), the extension of indication was accompanied by a change in dosing information for the initial indication. In the post-marketing phase, it may be equally important to emphasize finding the best dose for biologicals from an effectiveness *and* safety perspective rather than from a safety perspective only.

In conclusion, this study showed that in approximately one out of ten EMA-authorized biologicals, the recommended dose changed post-marketing for the initial indication. For the first extended indication, a dose difference between the initial and new indication was observed in one out of two biologicals. The dosing information for the extended indications was not changed during follow-up. In contrast with what previous research has reported for the dose of small molecules, the initial dose of biologicals was almost never reduced for safety reasons.

Competing Interests

There are no competing interests to declare.

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Appendix 1

List of included biologicals (n = 71)

Product	INN
Abasaglar	insulin glargine
Abseamed	epoetin alfa
Accofil	filgrastim
Adcetris	brentuximab vedotin
Arzerra	ofatumumab
Bemfola	follitropin alfa
Benlysta	belimumab
Binocrit	epoetin alfa
Biograstim	filgrastim
Biopoin	epoetin theta
Cimzia	certolizumab pegol
Cyramza	ramucirumab
Elaprase	idursulfase
Elonva	corifollitropin alfa
Entyvio	vedolizumab
Eperzan	albiglutide
Epoetin α-Hexal	epoetin alfa
Eporatio	epoetin theta
Extavia	interferon beta-1b
Eylea	aflibercept
Fertavid	follitropin beta
Filgrastim Hexal	filgrastim
Filgrastim ratiopharm	filgrastim
Gazyvaro	obinutuzumab
Ilaris	canakinumab
Increlex	mecasermin
Insulin Human Winthrop Rapid	insulin human
Jetrea	ocriplasmin
Kadcyla	trastuzumab emtansine
Krystexxa	pegloticase
Lemtrada	alemtuzumab
Lonquex	lipegfilgrastim
Lucentis	ranibizumab
Mircera	methoxy polyethylene glycol-epoetin beta

(continues)

Product	INN
Nivestim	filgrastim
NovoEight	turoctocog alfa
Nplate	romiplostim
Nulojix	belatacept
Nuwiq	simoctocog alfa
Opgenra	eptotermin alfa
Orencia	abatacept
Perjeta	pertuzumab
Plegridy	peginterferon beta-1a
Prolia	denosumab
Ratiograstim	filgrastim
Removab	catumaxomab
Retacrit	epoetin zeta
Revestive	teduglutide
Rilonacept Regeneron	rilonacept
Rixubis	nonacog gamma
RoActemra	tocilizumab
Ruconest	conestat alfa
Ryzodeg	insulin degludec/insulin aspart
Silapo	epoetin zeta
Simponi	golimumab
Soliris	eculizumab
Somatropin Biopartners	somatropin
Stelara	ustekinumab
Sylvant	siltuximab
Tevagrastim	filgrastim
Tresiba	insulin degludec
Trulicity	dulaglutide
Vectibix	panitumumab
Victoza	liraglutide
Vimizim	elosulfase alfa
Vpriv	velaglucerase alfa
Xgeva	denosumab
Xultophy	insulin degludec/liraglutide
Yervoy	ipilimumab
Zaltrap	aflibercept
Zarzio	filgrastim