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Initial prescriptions and medication switches of biological products: an analysis of prescription pathways and determinants in the Swiss healthcare setting

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ABSTRACT

Objectives Biological products have contributed to extraordinary advances in disease treatments over the last decade. However, the cost-saving potential of imitator products, so-called biosimilars, is still under-researched in Switzerland. This study aims to assess biosimilars' prescriptions at treatment initiation and their determinants, as well as biological therapy switches.

Design The study included all patients who had at least one biosimilar available on the market at the time when they were prescribed a biological product. We analysed longitudinal data for biosimilar prescriptions in Switzerland using descriptive statistics and logistic regression to quantify the associations with individual, pharmaceutical and provider-related variables.

Setting The analysis is based on de-identified claims data of patients with mandatory health insurance at Helsana, one of the Swiss health insurance companies with a substantial enrollee base in mandatory health insurance.

Participants Overall, 18 953 patients receiving at least one biological product between 2016 and 2021 were identified.

Outcome measures We differentiated between initial prescriptions and follow-up prescriptions. Our regression focused on initial prescriptions due to evidence indicating that patients tend to follow the medication prescribed at therapy initiation.

Results Although biosimilars' market share was low (28.6%), the number of prescriptions has increased (from 1016 in 2016 to 6976 in 2021). Few patients with medication switches (n=1492, 8.5%) were detected. Increased relative price difference (difference in the price of available biosimilars relative to price of corresponding reference product) was associated with decreased probability of biosimilar prescriptions, whereas male sex, an increase of available imitator drugs on the market, larger packaging sizes, and prescriptions from specialists or physicians in outpatient settings were associated with increased biosimilar use.

Conclusion The low number of biosimilar prescriptions, despite the proliferating biosimilar market, indicates a high potential for biosimilar diffusion. The findings indicate that patients typically adhere to the therapy options initially chosen and are less inclined to make changes following the initiation of treatment. Our research highlights the need for awareness initiatives to improve understanding among patients and physicians, enabling informed, shared decision-making about biosimilar prescriptions.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study evaluated the prescription of biosimilars using a broad set of sociodemographic, pharmaceutical, and healthcare provider variables and using a nearly representative database in Switzerland.
⇒ The study divided the medication treatment pathway into initial and follow-up prescriptions, with a specific focus on the initial prescriptions.
⇒ The study assessed determinants of initial prescriptions in the context of biosimilars.
⇒ Some demand-related factors (patients' health status, beliefs and experiences) and supply-related factors (physicians' incentives and beliefs) about biosimilars could not be accounted using the claims data.

INTRODUCTION

Biological products increased the spectrum of available treatment options considerably in the treatment of many cancers and autoimmune diseases. However, these medications are more expensive compared with many conventional synthetic drugs as they are produced by living cells and, thus, require a more complex manufacturing process. Currently, there are a considerable number of biologics in the final stages of development and approval.[1 2] The healthcare systems are likely to incur substantial costs even if just a small proportion of these biologics is granted market approval. One lever to curb rising drug costs is the replacement of biologics after patent expiration with less expensive imitator products, also known as biosimilars. Due to the biotechnological manufacturing process, exact copies of the biological products are not achievable. As a result, minor structural

deviations in the biosimilar are unavoidable,[3 4] and regulatory authorities accept them for market approval.[5 6]

A study conducted in the USA found that biologics can undergo price reductions ranging from −2.4% to −59.3% in response to biosimilar competition, with the extent of these reductions correlating with the adoption rate of biosimilars.[7] In Switzerland, a Swiss report has estimated a cost-saving potential of over SFr60 million for the complete replacement of reference products with biosimilars in 2019.[8] In the coming years, cost-saving potential will increase as several top-selling biologics will lose their patent protection in Switzerland[8 9] and corresponding biosimilars have already been approved in the European Union (EU).[2 10 11] However, the realisation of the cost-saving potential is assumed to be curbed because of scepticism about biosimilars from both the patient and physician side.[12–15] At the same time, patients and their healthcare providers seem to be less willing to switch biological products when therapy has already been started.[16–19] Consequently, the choice of initial prescription (IP) at therapy initiation is the decisive factor for following medication prescriptions. Despite the significant role of IP in shaping subsequent treatment pathways, research on the prescription behaviour of biological products at therapy initiation and the impact of IP is limited. Existing studies have only demonstrated that patients tend to remain on their initial biological treatment product once medication treatment has been initiated.[20] Thus, there is a need for further investigation into the influencing factors of IP and their influence on the choice of medication path. Thus, this study aims to assess biosimilars' prescriptions at treatment initiation and their determinants, as well as biological therapy switches.

METHODS

Study design and population

We studied adult patients (≥18 years) with at least one biological product claim between 2016 and 2021, insured by Helsana Group, a major Swiss health insurer (online supplemental table A1). The Helsana database covers 15% of Switzerland's population (1.2 million residents) and is regarded as representative, as prior research found minor differences between raw and adjusted results.[21 22]

In Switzerland, medication reimbursement is governed by the Federal Law on Health Insurance, which mandates that basic health insurance must cover the costs of essential medications. Swissmedic regulates the market entry of medications, while the Federal Office of Public Health oversees the establishment of the reimbursement list, which determines the extent to which a medication is reimbursed. Switzerland's medication reimbursement system aims to balance access to essential medications with cost control: to be eligible for reimbursement, medications must demonstrate efficacy, safety and cost-effectiveness compared with standard treatments. As such, all of the biological products included in this study are presumed to have fulfilled these requirements.

Measures

The study included all patients who had at least one biosimilar available on the market at the time of IP of a biological product. This enabled us to explore the determinants of non-prescription of biosimilars despite their availability. IPs were defined for each patient as claims that were not preceded by other prescriptions in the same medication category within the previous 24 months. Prescriptions that followed within 12 months were labelled as 'follow-up prescriptions' (FPs). By restricting the follow-up period to 12 months, we were able to focus on the medications that were prescribed as a result of the IP rather than medications that were prescribed for unrelated reasons. This approach allowed us to evaluate the impact of the IP more accurately on subsequent medication use. We selected 117 biological products approved by Swissmedic from a list (online supplemental table A1) derived from the Swiss Drug Compendium.

We considered patient characteristics as covariates, including sex, age group (<50, 50–64, 65–74, >74 years) and language region (German, French, Italian). We assessed comorbidity using the number of Pharmaceutical Cost Groups (PCGs) per patient (0, 1, 2, >2). PCGs are a recognised proxy for the presence of chronic diseases using data on medication bills that were reimbursed.[23] The Swiss healthcare system offers different cost-sharing options to patients, including low (SFr500, SFr1000) or high deductibles (ie, SFr1500, SFr2000 or SFr2500), and integrated care models, which offer premium rebates in exchange for limited healthcare provider options. Thus, having a low (SFr500, SFr1000) or high deductible (ie, SFr1500, SFr2000 or SFr2500 vs SFr300), and being enrolled in a managed care model were used in the analysis. Prescribed medications were characterised by category (fusion proteins, hormones, monoclonal antibodies, low-molecular-weight (LMW) heparins and growth factors), whether there were multiple packaging sizes, the cost per package of the reference product (in <SFr100, SFr100–599, >SFr600), relative price difference of the reference product to the corresponding biosimilar (<10, 10–19, >20) and the number of available imitator drugs (1, 2, >2) at the date of prescription. The analysis adds the aspect of healthcare provider by including information on the supply channel (general practitioner (GP), outpatient hospital, specialist, traditional pharmacy).

To ensure consistent terminology, we referred to all biologically manufactured drugs as 'biological products', while the originator drugs are referred to as 'biologics' or as 'reference products', and imitator products as 'biosimilars' throughout the manuscript.

Statistical analysis

All statistical analyses were performed at the study population that consisted of individuals who had at least one biosimilar available on the market at the time of IP of a biological product. All research participants' baseline characteristics are shown as counts and percentages, or as mean and SD for continuous variables. We compared

patient characteristics for all individuals with and without biosimilar IP. For bivariate comparisons between patients with and without biosimilar IP, Fisher's exact and X^2 tests were used accordingly. Statistical significance was defined as a two-sided p value of 0.05. We determined the biosimilar prevalence by distinguishing between IP and FP and the prevalence of biological therapy switches (number of prescriptions and patients) for each year (2016–2021). X^2 tests were used to determine whether the prevalence of biosimilars among all patients using a biological product was equivalent across the years. To assess the determinants of biosimilar prescriptions, we used logistic regression models in which the dependent variable was whether a biosimilar was prescribed as IP (0 or 1). We employed three distinct logistic regression models, each incorporating an additional set of variables, to comprehensively assess the impact of various factors on our study outcomes (online supplemental table A8). This approach allows us to explore multiple dimensions of influence and gain a more nuanced understanding of the relationships at play, enhancing the robustness and depth of our analysis. Both models B (sociodemographic+medication variables) and C (sociodemographic+medication+provider variables) show similar results and a better fit of the estimates compared with model A (sociodemographic variables) based on the goodness-of-fit criteria (Akaike Information Criterion, Bayesian Information Criterion). For the manuscript, we proceed with model C because we are mainly interested in the associations with biosimilar prescriptions from all three points of view (patient, medication, physician). ORs and corresponding 95% CIs were calculated for each regression coefficient. The success rate in the binomial model was denoted by the term 'occurrence' to improve the results' readability. All analyses were performed using R V.4.2.1.

Patient and public involvement

None.

RESULTS

This research was conducted using a study population comprising 68 310 individuals who received at least one prescription for a biological or biosimilar medication between 2016 and 2021. For our study, we eliminated individuals who did not maintain continuous mandatory health insurance coverage throughout the entire observation period. This exclusion was implemented to mitigate potential bias in our regression analysis, resulting in a remaining sample size of 53 379 patients. Within this subgroup, there were 18 953 instances of initial prescriptions for biological medications that had a biosimilar alternative available at the time of dispensing.

In the study sample, we observed 18 953 first prescriptions of biological products. Patient characteristics of the study population at the time of IP, stratified by type of IP (reference product 81.5%, biosimilar 18.5%), are presented in table 1. Female patients more frequently received biosimilars than male patients (60.6%). The study's overall population demonstrated a balanced distribution among age categories (<50, 50–64, 65–74, >74 years). Notably, individuals prescribed reference products as IP were more prevalent in the highest age group, while those initially prescribed biosimilars were more concentrated in the 50–64 and 65–74 age group. LMW heparins were the most prescribed reference products (54.2%), with growth hormones constituting the largest group of biosimilars (57.9%).

Table 2 describes the overall frequency of biological products over the observation period including the absolute and relative frequency of biosimilars in comparison with all biological prescriptions. Of all biological products (IP and FP), 28.6% were biosimilar prescriptions. In absolute values, the prescription rate of biosimilars increased over time (from 1016 in 2016 to 6976 in 2021). However, there is no discernible trend in the relative share of biosimilars in all prescriptions of biological products (35.5% in 2016, 39.2% in 2017, 45.2% in 2018, 41.6% in 2019, 26.3% in 2020 and 22.5% in 2021). Furthermore, the share of biosimilars in FPs was higher than in IPs in every year. The growth factor filgrastim was the most frequently prescribed active substance of biosimilars in IPs and FPs (53.1% and 36.2%, respectively), while enoxaparin was the most frequently prescribed active substance of reference products in IPs and FPs (65.3% and 25.5%, respectively) (online supplemental tables A2–A6).

Of the study population, only a small subset (n=1492, 8.5%) experienced at least one medication switch (table 3). Most patients had switches between reference products (n=867, 58.1%), followed by switches from reference product to biosimilar (n=331, 22.2%), from biosimilar to reference product (n=297, 19.9%) and switches between biosimilars (n=286, 19.2%). The number of patients with at least one switch increased between 2016 and 2021 (from 28 to 662), whereby the numbers of patients with switches between reference products increased most prominently (from 25.0% in 2016 to 62.1% in 2021). Switches between reference products and between biosimilars occurred most often for enoxaparin and rituximab, respectively (online supplemental table A7). The most common switches from reference product to biosimilar and from biosimilar to reference products were most often observed for filgrastim and enoxaparin.

As far as the regression results are concerned, the odds of prescribing biosimilars at IP have been increasing over the years (figure 1 and online supplemental table A8). Male sex was associated with 13.2% higher odds of receiving biosimilar IP, whereas residence in a French or Italian-speaking region had a 38.9% and 23.9%, respectively, lower occurrence of a biosimilar IP. None of the insurance-related variables showed a significant association with biosimilars' IPs. In terms of pharmaceutical variables, monoclonal antibodies, LMW heparins and growth factors were associated with substantially lower biosimilar IP occurrences (−88.5%, −99.9% and −84.2%) than fusion proteins. The availability of multiple

Table 1 Comparison of patient characteristics at IP between patients with reference product and biosimilar as IP

Variables, n (%)	Total	Patients with IP=reference product	Patients with IP=biosimilar	P value
Observations	18953	15453 (81.5)	3500 (18.5)	
Sex				
Male	7275 (38.4)	5895 (38.1)	1380 (39.4)	*
Female	11678 (61.6)	9558 (61.9)	2120 (60.6)	*
Age group				***†
<50 years	5501 (29.0)	4613 (29.9)	888 (25.4)	
50–64 years	4720 (24.9)	3764 (24.4)	956 (27.3)	
65–74 years	3963 (20.9)	3001 (19.4)	962 (27.5)	
>74 years	4769 (25.2)	4075 (26.4)	694 (19.8)	
Language region				***†
German	12719 (67.1)	9958 (64.4)	2761 (78.9)	
French	4324 (22.8)	3777 (24.4)	547 (15.6)	
Italian	1910 (10.1)	1718 (11.1)	192 (5.5)	
Number of comorbidities				**†
0	4738 (25.0)	3901 (25.2)	837 (23.9)	
1	3295 (17.4)	2664 (17.2)	631 (18.0)	
2	3072 (16.2)	2448 (15.8)	624 (17.8)	
>2	7848 (41.4)	6440 (41.7)	1408 (40.2)	
Deductible				***†
Low	15765 (83.2)	12846 (83.1)	2919 (83.4)	
High	3188 (16.8)	2607 (16.9)	581 (16.6)	
Managed care	11921 (62.9)	9790 (63.4)	2131 (60.9)	***
Category				***†
Fusion proteins	360 (1.9)	178 (1.2)	182 (5.2)	
Hormones	2112 (11.1)	1697 (11.0)	415 (11.9)	
Monoclonal antibodies	2908 (15.3)	2107 (13.6)	801 (22.9)	
LMW heparins	10272 (54.2)	10196 (66.0)	76 (2.2)	
Growth factors	3301 (17.4)	1275 (8.3)	2026 (57.9)	
Multiple package sizes	16432 (86.7)	13532 (87.6)	2900 (82.9)	***†
Cost per package of reference product (in SFr)				***†
<100	9866 (52.1)	9652 (62.5)	214 (6.1)	
100–599	5066 (26.7)	3179 (20.6)	1887 (53.9)	
>600	4021 (21.2)	2622 (17.0)	1399 (40.0)	
Relative price difference (%)				***†
<10	13807 (72.8)	11546 (74.7)	2261 (64.6)	
10–19	2386 (12.6)	1871 (12.1)	515 (14.7)	
>20	2760 (14.6)	2036 (13.2)	724 (20.7)	
Number of available imitator drugs				***†
0	–	–	–	
1	12490 (65.9)	12012 (77.7)	478 (13.7)	
2	2741 (14.5)	1911 (12.4)	830 (23.7)	
>2	3722 (19.6)	1530 (9.9)	2192 (62.6)	
Supply channel of first prescription				***†
General practitioner	1185 (6.3)	1097 (7.1)	88 (2.5)	

Continued

Table 1 Continued

Variables, n (%)	Total	Patients with IP=reference product	Patients with IP=biosimilar	P value
Outpatient hospital	6224 (32.8)	4359 (28.2)	1865 (53.3)	
Specialist	3606 (19.0)	2674 (17.3)	932 (26.6)	
Traditional pharmacy	7564 (39.9)	6981 (45.2)	583 (16.7)	
Rest	374 (2.0)	342 (2.2)	32 (0.9)	

Significant codes: *p<0.05 **p<0.01, ***p<0.001.
*Fisher's exact test.
†X^2 test.
IP, initial prescription; LMW, low-molecular-weight.

packaging sizes was associated with 4.6-fold higher odds of biosimilar IP compared with medications with solely one packaging size. For the absolute package price, no consistent pattern was observed, as medications with prices between SFr100 and SFr599 per pack decreased the odds by 79.8% compared with the baseline (<SFr100), whereas the odds in the highest prize category (>SFr600) were lower by 34.3%. However, compared with products with a <10% price difference between reference product and biosimilar, higher price reductions were associated with decreased occurrence of biosimilar IP: medications with 10–19% price difference had 92.4% lower odds and medications with more than 20% had even 93.3% lower odds. On the contrary, increasing the number of available imitator medications of prescription (2 and >2) had substantially higher (2.36-fold and 9.65-fold) odds of biosimilar IP compared with prescriptions with only one available biosimilar. As far as provider variables are concerned, physicians in the outpatient hospital setting prescribed far more biosimilars compared with GPs (2.48-fold higher odds). The occurrence of biosimilar IP was also 41.7% higher in patients who had been prescribed biological products by a specialist than in patients who had received the equivalent medications from a GP.

DISCUSSION

The increase in biosimilar prescriptions over time can be attributed to the growing biosimilar market. With 15 approved biosimilars in 2016, this market has expanded significantly, reaching 78 biosimilars in 2021 (online supplemental table A1).[8 20] A longer time on the market gives the biosimilar a better chance to establish itself and gain market share. Despite this growth, the biosimilars' claims in Switzerland remained relatively low. In 2021, claims for reference products were four times higher than claims for biosimilars among all available biological products with biosimilars.[8] Comparatively, other countries like Norway have achieved 80% biosimilar quota of all biological products,[24] while in Germany, studies reported an average biosimilar ratio between 40.5% and 51.9% in 2019.[25 26] In the present study, we observed substantially lower average biosimilar quota of 28.0%. Infliximab is a particularly compelling example, with the biosimilar

Table 2 All prescriptions for which a biosimilar was approved at the time of the prescription

	Total	2016	2017	2018	2019	2020	2021	
IP								
n	18953	815	888	1037	1520	5313	9380	
Biosimilars (n, % of N)	3500 (18.5)	262 (32.1)	343 (38.6)	391 (37.7)	612 (40.3)	813 (15.3)	1079 (11.5)	****
FP								
n	50251	2047	2716	3314	6306	14288	21580	
Biosimilar (n, % of N)	16293 (32.4)	754 (36.8)	1071 (39.4)	1578 (47.6)	2644 (41.9)	4349 (30.4)	5897 (27.3)	****
Total (FP+IP)								
n	69204	2862	3604	4351	7826	19601	30 960	
Biosimilars (n, % of N)	19793 (28.6)	1016 (35.5)	1414 (39.23)	1969 (45.25)	3256 (41.60)	5162(26.34)	6976 (22.53)	****

Significant codes: ***<0.001.
*X^2 test.
FP, follow-up prescription; IP, initial prescription.

Table 3 Patients with biological therapy switches

Switches, N=patients	Total	2016	2017	2018	2019	2020	2021	P value
At least one, n	1492	28	42	77	249	434	662	
Reference product to reference product, n (%)	867 (58.1)	7 (25.0)	15 (35.7)	37 (48.1)	146 (58.6)	251 (57.8)	411 (62.1)	****
Biosimilar to biosimilar, n (%)	286 (19.2)	9 (32.1)	10 (23.8)	14 (18.2)	51 (20.5)	74 (17.1)	128 (19.3)	*
Reference product to biosimilar, n (%)	331 (22.2)	6 (21.4)	11 (26.2)	21 (27.3)	60 (24.1)	103 (23.7)	130 (19.6)	*
Biosimilar to reference product, n (%)	297 (19.9)	10 (35.7)	8 (19.0)	15 (19.5)	49 (19.7)	96 (22.1)	119 (18.0)	*

Significant codes: ***<0.001.
*X^2 test.

share reaching 26% in Germany after only 12 months on the market (2017) and rising to 64–68% of the biosimilar market in 2019. By contrast, infliximab achieved a market share of only 22% in Switzerland in 2019.[8]

The low biosimilar market share in Switzerland can be attributed to several factors, including physician and patient knowledge deficits regarding biosimilars, leading to reluctance in their use.[12–15] According to survey studies,[17 27–30] negative perceptions of biosimilars among 15–30% of the population may be rooted in concerns about the evidence base for their efficacy and safety, primarily requiring bioequivalence for approval. However, there is increasing evidence of equivalent safety and efficacy of biosimilars, along with evidence of bioequivalence.[31–33] Furthermore, a challenge for newly approved biosimilars is the difficulty in extending conclusions from randomised controlled trials (RCTs) to the broader population that will use the biosimilar. This is because RCTs typically enrol a more homogeneous population, and certain patient groups, such as paediatric, elderly and comorbid populations, as well as patients with polypharmacy, are often under-represented in these trials.[34–36] As a result, prescribers may be sceptical about the use of biosimilars in these patient populations because of the lack of data.

Moreover, the finding that patients frequently switch from biosimilar to reference products underscores the complex landscape surrounding biosimilar utilisation. This phenomenon may, in part, be influenced by the current incentive system that discourages the prescription of biosimilars for self-dispensing doctors and pharmacies as they are rewarded with larger profit margins for prescribing the more expensive products.[8] Conversely, under a capitation payment model, managed care physicians may have a financial incentive to prescribe lower-cost biosimilars in order to maximise profits. However, if physicians are not properly educated about the safety and efficacy of biosimilars, they may be hesitant to prescribe them.

That only a small subset (n=1492, 8.5%) experienced at least one medication switch can be explained by the reluctance of patients to switch to a biosimilar medication due to the fear of experiencing new and unknown side effects. Patients who have been using a particular medication for a long time and have become accustomed to its efficacy and safety profile may be hesitant to switch to a biosimilar, which they perceive as being different and possibly inferior. Nevertheless, efficacy of biosimilar switching has been observed.[8 18 31–33 37] According to a systematic literature review based on 90 published studies, the great majority of the publications did not report differences in immunogenicity, safety or efficacy when patients switched to biosimilars. Three large studies did not show differences in efficacy or safety after multiple switches between reference product and biosimilar.[38–40] Only two publications reported a loss of efficacy or increased dropout rates.[41 42] Often, this very knowledge and awareness about the safety and efficacy of switching to new treatment options lack for prescribing physicians who rely on solid, evidence-based data to make treatment decisions.[43–45] The substantial transition from biosimilars to reference products observed in our study warrants discussion. While our analysis did not delve into the specific drivers behind this shift, several factors may contribute to it. These

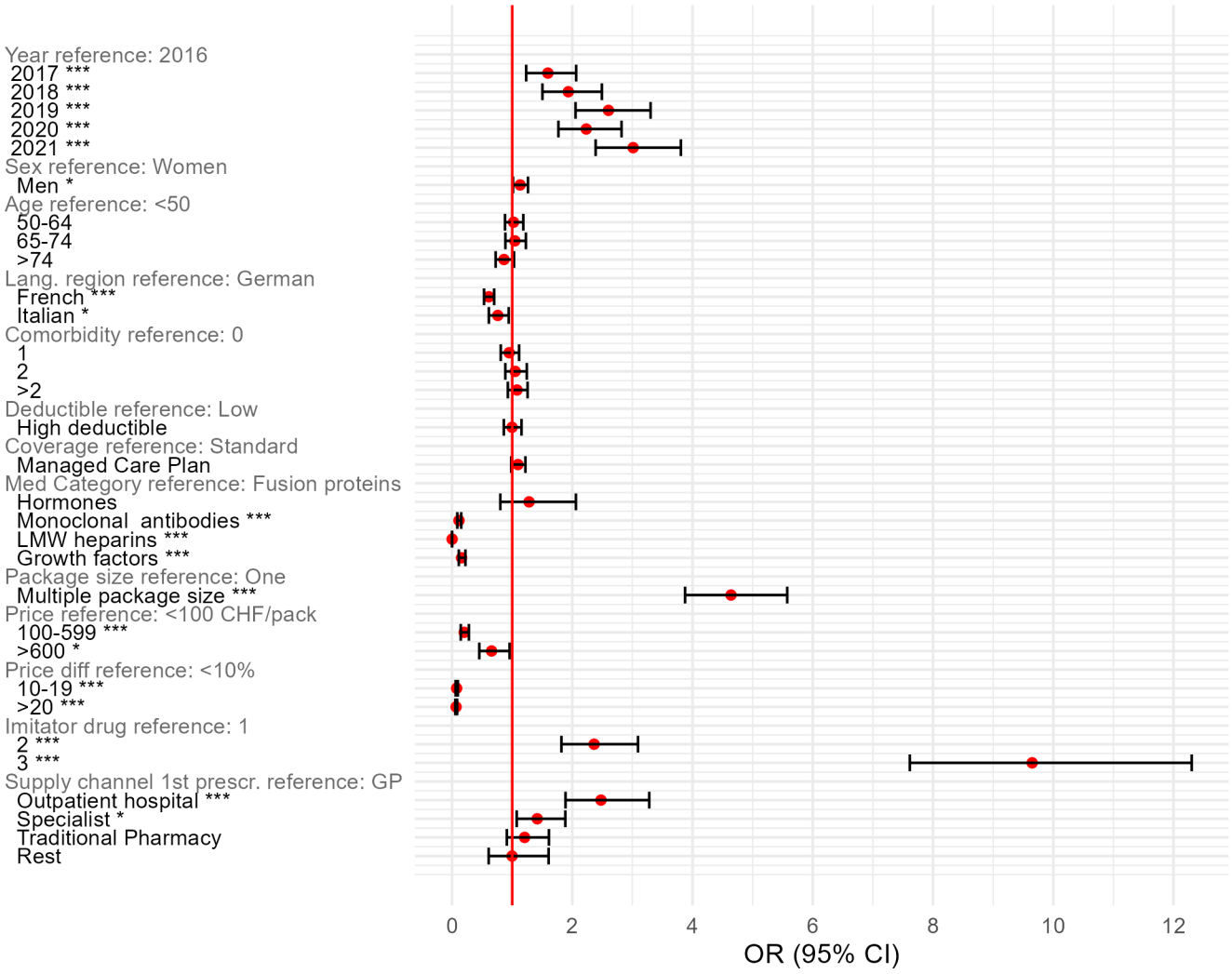

Figure 1 Determinants of biosimilar initial prescription (logistic regression). CHF, Swiss franc; GP, general practitioner; LMW, low-molecular-weight. *p<0.05 **p<0.01, ***p<0.001.

could encompass the aforementioned patient and physician preferences. Further exploration of these factors is essential to gain a comprehensive understanding of the dynamics between biosimilars and reference products in clinical practice, shedding light on the implications for healthcare stakeholders and policymakers.

The regression results revealed that biosimilar IP rates were lower in French-speaking cantons. These regional variations may be caused by a variety of variables, including a higher concentration of medical services in urban regions, various patient characteristics and cultural variations between cantons.[46 47] Our findings showed that biosimilars with high relative price difference to reference product were less likely prescribed. Several factors contribute to physicians' reduced prescription rates in association with the lower prices of biosimilars. A possible explanation is that healthcare providers may have less experience with biosimilars with a higher price difference or may perceive them as less established and less proven than biosimilars with a lower price difference. This lack of familiarity or perceived risk may contribute to reluctance in prescribing biosimilars with a higher price difference. It is also important to consider the role of financial incentives and reimbursement policies in biosimilar prescribing: currently, dispensation channels receive a larger profit margin when distributing the more expensive reference product under the present price-dependent margin.[20] This incentive system seems to be characteristic for Switzerland, as studies conducted in European countries did not find a relationship between price difference and biosimilar dissemination.[48–50] This might be attributed to several factors that differentiate Switzerland from other European countries: cantonal differences in self-dispensing regulation, the country's different prescribing cultures and guidelines across its language regions, and capitation is implemented only in relatively few cases in Switzerland. In our analysis, male patients had more biosimilar IP. According to studies, women were often more sceptical of imitator drugs[27 51–54] and they more frequently believe that they are more responsive to medications than men.[55–57] This can have an impact on their confidence in biosimilars, making female patients more aware of potential side effects or lack thereof. Biosimilar IPs were prescribed more frequently

for fusion proteins compared with other categories which indicates an increased acceptance of imitator products in this drug class. This is supported by the relatively early market entry (2018) and by a meta-analysis showing comparable results in terms of efficacy and safety between reference product and biosimilars.[58] The strongest facilitator of biosimilar prescriptions was the amount of available biosimilars, which is in line with the findings of a prior study.[48 59] Thus, the replacement of reference products by biosimilars seems to be better accepted in market segments with many imitator products. This finding is probably associated with the larger collective promotional effort from multiple players involved in the field to favour biosimilars; it is noteworthy that the largest adoption of biosimilars (filgrastim) has been partially attributable to the fact that numerous biosimilar producers have commercialised different products, whereas there is only one company branding the reference product.[60] We found more biosimilar IPs for specialists and outpatient hospital physicians than GPs. These findings are in line with existing literature that showed more biosimilars from specialists who reported a higher confidence in the comparability of biosimilars than GPs.[61 62] Differences in care providers may be due to a variety of reasons: some healthcare providers may not be interested in stockpiling too many different medications and additional biosimilars, as they sometimes have large storage requirements (cooling, expiration date) and, thus, are associated with a significant financial risk.[20] In addition, it has been demonstrated that the dissemination of knowledge about new prescription options is heterogeneous because there are large learning costs associated with the treatment effects of new therapy options, which rely on the training and experience of the doctor.[63] Despite the fact that a previous study conducted in the context of generic drugs showed that older people are less likely to use imitator products when offered a choice,[27 59] we did not observe an age dependency of biosimilar prescriptions.

The most valuable strength of this study is the extensive dataset of biosimilar prescriptions and potential influencing factors including sociodemographic, pharmaceutical and healthcare provider variables that were gathered from a representative sample of the Swiss population. Hence, earlier research has suggested that this database can be considered reasonably representative of the broader Swiss population, given that the findings revealed only minimal disparities between unadjusted and adjusted results. The main limitation is the dearth of clinical data in our database (eg, disease severity, clinical diagnosis and reason for biosimilar utilisation). However, we attempted to mitigate this by using comorbidity measures based on reimbursed prescriptions to control for potential confounders. Furthermore, it is possible that invoices from individuals whose annual healthcare expenses did not surpass the annual deductible were not included in the analysis. Nevertheless, internal analyses conducted by Helsana indicated that this proportion accounts for approximately 1.5% of invoices, suggesting that any potential selection bias is likely minimal. Another limitation of our study is that the follow-up period for the prescriptions was limited to 12 months. This time frame may have led to the exclusion of some prescriptions, potentially introducing bias into our results. Nevertheless, we observed that a significant number of patients (7608, which accounts for 43.1% of the total) were given only one prescription, indicating that any bias arising from this limitation is expected to be insignificant.

It is worth noting that the actual biosimilar quota (proportion of biosimilar claims relative to overall biological product claims) is lower in reality as there are biological products for which no corresponding biosimilars are available on the market. Nevertheless, even when considering this relatively higher observed quota, it remains comparatively low compared with other EU countries. This has important implications for the adoption and utilisation of these products in Switzerland. Patients and physicians should be better and objectively informed about biosimilars in order to increase the acceptance.[45 46] Also, for example, a clear and conspicuous indication of the prescribed active substance on the medication package for both the reference product and the imitator drug, for instance, could enhance patient confidence.[40] To address the perceived uncertainty and mistrust in imitator products, the evidence base should be further strengthened: direct evidence to help explain some of the practical aspects related to the use of biosimilars can be provided by retrospective studies, national databases and registries that track the long-term immunogenicity and safety of biosimilars.[64–69] In addition, the incentive system for healthcare providers seems to be designed in such a way that fewer biosimilars are prescribed. Thus, these incentives should be eliminated, for example, by introducing a fixed margin that always remunerates the medication supplier the same regardless of the prescribed product (reference product or biosimilar). In order to exploit the cost-saving potential of biosimilars, the aforementioned measures should be targeted to biosimilars with a noticeable price difference compared with their reference products, and that still possess relatively low biosimilar market share. Taking into account the findings presented in online supplemental table A6, notable examples of these biosimilars include bevacizumab, follitropin alfa and pegfilgrastim.

However, the decision to prescribe an imitator drug should not merely be motivated by the cost-saving potential but should ensure appropriate healthcare provision for the patients. Therefore, it is crucial for healthcare providers to engage in shared decision-making with their patients to determine the most appropriate treatment option based on their individual medical situation.

CONCLUSION

Despite an increase of available biosimilars in Switzerland between 2016 and 2021, the biosimilar market share remained relatively low over time. In addition, biological

therapy switches were rarely observed, highlighting the importance of IPs. Our study suggests that greater acceptance and higher utilisation of biosimilars may be associated with the availability of different package sizes and lower price differences between biosimilars and their reference products. Patients and providers should be informed about biosimilars in a timely and appropriate manner, and outdated incentive structures have to be changed to increase the use of biosimilars.

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Ethics approval The data used in this study were retrospective, pre-existing, de-identified and anonymous in accordance with privacy laws and regulations. This study was free from the provisions of the Swiss Federal Law on Human Research because it used retrospective, de-identified and anonymised data [70] and was thus exempted from receiving clearance from the regional ethics committee (the ethical committee of the Canton of Zurich) as well as from obtaining the patients' informed consent.

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