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COMMENTARY: LOCAL POLICIES ON BIOSIMILARS - ARE THEY DESIGNED TO OPTIMIZE USE OF FREED RESOURCES; findings and implications?

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Abstract
There is an increasing need to prescribe biosimilars to fund new medicines and increasing medicine volumes. Bertolani and Jommi document successful measures introduced regionally in Italy.

Body of the Commentary
The recent GABI Journal article by Bertolani and Jommi comprehensively assessed the implications of a range of policies including education, benchmarking, and financial incentives, implemented by the different healthcare organisations (HCOs) among the Regions in Italy to increase the use of biosimilars as a way to conserve resources. This included both prospective and retrospective analyses of shifts in prescribing behaviour among the different regions and potential savings generated as well as how the savings generated were used (1).

We reviewed the paper by Bertolani and Jommi (1) and linked these findings with other recent studies in an attempt to stimulate ongoing debate regarding potential ways to enhance the future use of biosimilars as well as how best to utilize the considerable resource savings produced (2, 3) without compromising care.

The Bertolani and Jommi study is seen as particularly important as a source of information that can be used to provide future guidance as there have only been a limited number of studies to date that assessed differences in regional policies to enhance the prescribing of biosimilars in the ambulatory care setting where biologicals are increasingly being used (4). A response rate to the survey of 38% is seen as acceptable (5, 6), especially since the Regions surveyed covered 93% of the Italian population (1).

The need to leverage competition from biosimilars will only increase since without a major increase in the use of biosimilars global expenditure on medicines is projected to reach US$1.5 trillion by 2023 (7-9).This growth will be primarily driven by increased expenditures on specialty biological medicines, including new medicines for chronic, complex, or rare diseases such as cancer and orphan diseases. Global expenditure for these medicines is likely to reach 50% of total medicine expenditures in the near future (7, 10). Such expenditures are difficult to sustain, especially in countries with universal healthcare systems that need to fund a growth in the use of medicines driven by increasing rates of non-communicable diseases, changes in clinical practice, and the launch of new, high-priced medicines that address areas of unmet need (11-14). There are additional concerns raised about

some new, high-priced medicines for cancer and orphan diseases, for which funding appears driven more by the emotive nature of these diseases than by their proven clinical benefits (15-18). Their value is being increasingly questioned a as more medicines advocated in guidelines become available as low cost, multiple sourced medicines or biosimilars (19-21).

Biological medicines under increasing scrutiny include Humira® with global sales of US$19.9 billion in 2018. Although Humira® sales are now being decreased, especially in Europe, through increasing use of lower priced biosimilars as well as by the fact that AbbVie lowered the price of Humira® to compete (22-26). For example, among Danish hospitals, expenditures for adalimumab decreased by 82.8% following the availability of biosimilars with almost total replacement by biosimilars (95.1% utilisation). In the UK, expenditure on adalimumab is envisaged to fall by 75% following the availability of biosimilars (23, 25). Such reductions are welcomed, especially among lower- and middle-income countries, including Central and Eastern European countries, where the use of biologicals has been limited by available governmental resources as well as by high patient co-payments (27-29). Biosimilar switching programmes have been shown to conserve resources by a number of studies that also were unable to demonstrate meaningful differences in effectiveness or safety between biosimilars and originators. Such studies have included infliximab and other biologicals across a range of indications (30-38). There have however been some concerns requiring patient monitoring (39, 40). Such concerns could be exacerbated by multiple modifications in the manufacturing of originator biologic drugs that can occur without companies being required to undertake clinical studies to assess the effect of such changes on clinical outcomes in actual practice, even with major manufacturing changes (41, 42).

Other biological medicines of special interest to health authorities across Europe and beyond include rituximab, infliximab, and etanercept with current global sales of US$7.9billion, US$ 5.9 billion and US$ 5.8 billion in 2017 respectively (43-45). These concerns persist despite the fact that these sales are being reduced as the result of the increasing use of lower cost biosimilars (38, 39, 45-49). Global sales of Herceptin® (trastuzumab) were stable in 2019 at US$7billion due to increasing use of biosimilar trastuzumab. The use of biosimilar trastuzumab is expected to continue to increase globally. Trastuzimab biosimilars have already captured 45% of the European market (50-52). However, these savings are being offset by growing expenditures on pertuzumab in combination with trastuzumab; with annual sales of US$2.8billion in 2019 as well as by the use of Kadcyla® (trastuzumab emtansine), which is expected to reach annual sales of US$4.94billion by 2023 (50, 53).

Another important biologic is long acting insulin glargine used principally for patients with Type 1 diabetes. The insulin glargine market was valued at approximately US$3.88 billion in 2018, and is envisaged to reach US$9.26 billion by 2025 (54). However, potential savings associated with the introduction of biosimilar insulin glargine have been hampered by limited price reductions seen in practice in a number of countries. There are also concerns with switching because differences in devices between manufacturers could increase the rate of hypoglycaemia (55-58). These concerns have resulted in some health authorities advising against switching, despite similar effectiveness and safety being demonstrated in studies comparing the originator and a biosimilar (55, 56, 59-62). The situation is however changing, at least in the US, where biosimilar insulin glargine reached over 40% of market share in the US Medicaid programme in 2018. There are also a number of initiatives and publications pushing for increased use of biosimilars among European countries including those encouraging new patients to be started on a biosimilar (49, 63-66).

A number of published studies have shown the potential for considerable savings from biosimilars. These results are pushing health authority to employ initiatives to enhance their use (3, 9, 38, 49, 51, 67-70). Winegarden (2019) in the US estimated annual savings of up to US$7billion from the use of a range of biosimilars, and that these savings are likely to grow as more biosimilars become available (3). However for maximum savings, both supply- and demand-side measures are needed (21, 69). This has been shown in studies of oral generic medicines comparing potential policies and savings in Korea with those in the UK (71-74). Multiple demand- and supply-side measures in Scotland resulted in a considerable reduction in expenditure on lipid lowering medicines and proton pump inhibitors despite appreciably increased volumes (73, 74). Moorkens *et al.* (2017), Rémuzat *et al*. (2017) and Vogler *et al.* (2017) have all recently summarised ongoing demand-side measures in Europe to enhance the use of biosimilars. Simoens *et al.* (2018) also provided guidance on additional demand-side measures that could be introduced to further realise the benefits of biosimilars (75-78). There are European countries where some lower cost biosimilars now account for the total market, e.g. EPO

and G-CSF (79).and countries such as France and the UK are actively working to increase biosimilar penetration rates (80, 81).

Brill in the US has recently discussed the benefits of shared savings to enhance biosimilar use among State Medicaid programmes (10). Siu *et al.* (2019) documented ongoing activities to enhance the use of biosimilars in both the private and public sectors in Canada (70). These activities include preferential coverage by private insurers for increasing use of biosimilars, the pan-Canadian Oncology Biosimilars Initiative to enhance adoption of biosimilars in oncology (an attempt to address concerns with funding in oncology), as well as the British Columbia Biosimilars Initiative in May 2019 that promotes switching, with the savings used to lower premiums and co-pays where pertinent (70). In addition, Biosimilars Canada has recently developed a centralised patient support service platform to assist manufacturers and patients with increasing the use of biosimilars (70). Such activities are needed to promote the use of biosimilars because originator manufacturers have been appreciably lowering prices of their originators just before patent expiry to dissuade biosimilar companies from entering the market. (22, 44, 79) Suggestions have been made that originator companies should automatically lower their prices following patent expiry, thereby negating the need for biosimilars to interfere with the market in the first place. (82) Methods are needed to counter other behaviors of originator companies such as developing new formulations just before patent expiry to create a barrier to biosimilars mirroring other evergreening tactics (79, 83).

It was impressive to see that 89% of HCO surveyed by Bertolani and Jommi had implemented policies to enhance the use of biosimilars (1). Educational activities were particularly prominent, increasing in recent years, including information on market access pathways for biosimilars as well as the results of tenders. Educational activities are crucial to allay fears regarding the effectiveness and safety of biosimilars. These fears are illustrated in Italy by the seven scientific Italian societies that recently expressed concerns about the Regional Administrative Court of Piemonte promoting the automatic substitution of biologicals in terms of therapeutic continuity for patients and concerns with the freedom of clinicians (84). Despite this, benchmarking of biosimilar prescribing among physicians was already taking place among 75% of HCOs surveyed and this is likely to grow since such benchmarking of physician prescribing is working well in other countries (1, 85). The 62% of HCOs that also provided physicians with prescribing targets for biosimilars is similar to what has been seen in other countries and regions (86-88), with 68% and 24% respectively introducing incentives and sanctions to improve prescribing rates. Sanctions include monetary sanctions and potentially removal of the right to prescribe (1).

A concern though is that patients were involved in educational/ information programmes among only 22% of the HCOs surveyed (1). This is a potentially important weakness since all key stakeholders need to be convinced about the value of biosimilars in order to reduce any potential nocebo effects (89, 90).

The study of Bertolani and Jommi adds to a number of examples of successful multiple demand-side measures including preferentially encouraging the prescribing of multiple sourced medicines versus originators and patented medicines in a class without compromising care (91-93). Monies saved can subsequently be used to fund new more expensive medicines as well as other healthcare services such as diagnostics. 93% of HCOs also provided physicians with information retrospectively or prospectively on potential savings from increased use of biosimilars, with 25% of HCOs also participating in post-marketing studies to help further address potential fears with biosimilars (1). However only 21% of HCOs systematically estimated the proportion of potential patients not receiving biosimilars, with only rare perceptual surveys among patients and other healthcare professionals. This situation may need to change given the stated concerns of the seven scientific Italian societies (84).

In conclusion, Bertolani and Jommi, have provided a comprehensive review of ongoing policies among HCOs in the different regions of Italy and their potential to influence on future directions. This information is useful for other countries where demand-side measures can be localised to meet future goals, with the potential for localities to learn from each other. This is important to stimulate increasing use of biosimilars in a way that addresses the accelerating resource challenges brought about by the expanding use of medicines in ageing populations as well as the need to pay for new, high-priced medicines that address areas of previously poorly or untreatable diseases.

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The authors have no conflicts of interest to declare.

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