# Diverging Impacts of Evergreening and Biosimilars on Trastuzumab Utilization and Costs in South Korea : Implications for Sustainable Access and Market Competition

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## Introduction

- Biologics remain among the most expensive therapeutic classes, posing persistent challenges to the sustainability of healthcare financing.
- While biosimilars aim to improve affordability, originator companies often employ evergreening strategies, like subcutaneous (SC) formulations, to maintain market share.

## Objective

- Using Trastuzumab, South Korea's first approved anticancer biosimilar, this study examines how these competing strategies shaped utilization trends, market restructuring, and healthcare expenditures.

## Methods

| | Market-level Data | Patient-level Data |
|---|---|---|
| **Data source** | IQVIA™<br>Covers approximately 95% of the global prescription drug market across more than 90 countries | K-CURE<br>* Korean Clinical Data Utilization Network for Research Excellence<br>A representative 10% breast cancer sample of Korean patients, linked to staging and mortality |
| **Data period** | ▪ Q1 2013 – Q2 2020 (30Q) | ▪ Q1 2013 – Q4 2019 (28Q) |
| **Variables** | ▪ Sales volume<br>mg converted from standard units (SU; number of standard "dose" units sold)<br>▪ Manufacturer-level sales value<br>USD, log-transformed, Inflation-adjusted to 2017 (Korea CPI) | ▪ Claims<br>One treatment episode per claim<br>▪ Patient counts<br>▪ Healthcare costs<br>Log-transformed, per patient per year (PPPY), using 2017 avg. exchange rate (1 USD = 1,130.5 KRW) |
| **Intervention Point** | 2013 1Q; SC launch (2014Q4); Biosimilar entry (2017Q3); 2019 4Q; 2020 2Q | |

**Patient selection**

Breast cancer patients registered in the K-CURE Public Cancer Staging Investigation Database (2013–2019)
**N= 16,870**

Excluded :
1. **Patients with incomplete data** (N=144)
2. **Patients diagnosis of other primary cancers within one year of breast cancer diagnosis** (N=1,620)
3. **Patients who self-reported prior cancer history before registration** (N=1,135)
4. **Male breast cancer patients** (N=49)
5. **Patients who absence of any documented medication use within 12 months post-diagnosis** (N=1)

Eligible breast cancer patients after initial exclusions
**N= 13,921**

Excluded (trastuzumab-specific selection) :
1. **Patients with HER2-negative or unknown hormone receptor status** (N=10,157)
2. **Patients who had received trastuzumab prior to diagnosis** (N=1)
3. **Patients who did not receive trastuzumab within one year after diagnosis** (N=1,512)

Final study cohort
**N= 2,251**

### Statistical analysis

- We conducted segmented regression analyses using ARIMA/SARIMA models.

$$Y_t = \beta_0 + \beta_1 \cdot time_t + \beta_2 \cdot SC_t + \beta_3 \cdot time\_after\_SC_t + \beta_4 \cdot Biosimilar_t + \beta_5 \cdot time\_after\_Biosimilar_t + z_t$$

- Optimal model specifications were selected using the auto.arima( ) function from the R forecast package.
- All statistical tests were two-tailed, and p-values less than 0.05 were considered statistically significant.

$Y_t$ : Each outcomes (Sales volume, Claims, Sales value, Patient counts, Healthcare costs)
$\beta_{2,4}$ : immediate level change following the intervention
$\beta_{3,5}$ : the change in slope following the intervention

## Results

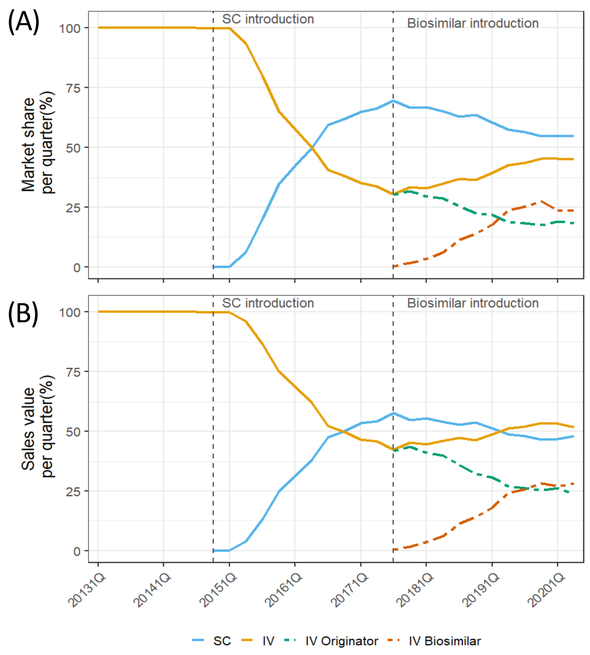


**Figure 1.** Quarterly trastuzumab market share and sales value (%) in South Korea using IQVIA-MIDAS (2013Q1–2020Q2)

### Utilization Impact of SC Introduction

- IV sales volume steadily declined following SC introduction
- SC sales rapidly increased, surpassing IV in Q3 2016
- SC peaked at 69.6% market share just before biosimilar entry
- **Total trastuzumab** : Significant slope increase (190,148 mg/quarter) of total sales volume following SC introduction
- **IV trastuzumab**: Trend shifted from growth to significant decline (–645,279 mg/quarter)
- **SC trastuzumab**: Sharp growth acceleration (+698,520 mg/quarter)
- **Claims**: Steeper slope increase (+26.596 claims/quarter)
- **Patient counts**: Positive slope increase (+6.285 patients/quarter)

### Utilization Impact of Biosimilar Introduction

- IV experienced partial recovery, reaching 45.3% market share by Q1 2020
- IV biosimilars overtook IV originator in Q2 2019 (biosimilar: 23.8% vs. originator: 18.8%)
- SC maintained dominance with 54% market share in 2020
- **Total trastuzumab** : Additional slope acceleration (+106,815 mg/quarter)
- **IV trastuzumab**: Trend reversal with sustained recovery (+754,099 mg/quarter)
- **SC trastuzumab**: Growth rate markedly slowed but slope remained positive (+67,420 mg/quarter)
- **Claims**: Decline in growth rate (–24.645 claims/quarter)
- **Patient counts**: Slope decrease (–7.220 patients/quarter)

### Expenditure Impact of SC Introduction

- SC rapidly gained value share, surpassing IV in Q4 2016
- SC stabilized above USD 9 million per quarter
- IV sales value showed continuous decline
- **Total trastuzumab** : Market value reversed with slope decline (–4.5% per quarter)
- **IV trastuzumab**: Significant slope decline (–12.54% per quarter), shifting from growth to sustained decrease
- **SC trastuzumab**: Sharp initial growth (+89.65% per quarter)
- **Total per-patient-per-year &Breast cancer-related expenditure** : Maintaining previous upward trends

### Expenditure Impact of Biosimilar Introduction

- Biosimilars reached 28.2% of total market value by Q4 2019
- SC maintained substantial value share (48.2% by Q2 2020)
- IV biosimilars overtook IV originator by Q4 2019
- **Total trastuzumab** : Slope recovery (+3.25% per quarter)
- **IV trastuzumab**: Partial offset by biosimilar entry (+5.97% slope increase)
- **SC trastuzumab**: Significant deceleration (–56.0% slope decrease)
- **Total per-patient-per-year:** Slope increases (+1.11% per quarter)
- **Breast cancer–related expenditure**: Sustained growth acceleration (+1.41% slope increase per quarter)

### Key Findings Summary

✓ SC introduction maintained 54% dominance despite biosimilar competition.

✓ IV biosimilars achieved limited recovery while SC preserved substantial value share.

✓ Market expansion through segmentation rather than substitution, with biosimilars competing within existing IV segments.

**Table 1.** Segmented regression estimates of quarterly changes in trastuzumab utilization following the introduction of subcutaneous (SC) formulation and intravenous (IV) biosimilar entry

| Segmented Term | Trastuzumab sales volume (1,000mg/quarter) | | | | Patient-level Trastuzumab utilizaiton | |
|---|---|---|---|---|---|---|
| | Total | IV | IV originator | SC‡ | Total claims | Number of patients |
| Slope before intervention | 210.109** | 233.336* | 214.570* | 698.520*** | 1.626 | 2.442 |
| **Introduction of SC Trastuzumab†** | | | | | | |
| Step change after intervention | -275.323 | 581.266 | 743.950** | - | 82.914*** | 12.571 |
| Slope change after intervention | 190.148** | -645.279*** | -647.430*** | - | 26.596** | 6.285* |
| **Introduction of Trastuzumab biosimilar†** | | | | | | |
| Step change after intervention | -1593.320*** | -778.842** | -291.740 | 338.180 | -19.626 | -5.566 |
| Slope change after intervention | 106.815*** | 754.099*** | 389.640*** | -631.100** | -24.645*** | -7.220*** |

- ARIMA specification: Total trastuzumab = (3,0,0); IV Ttrastuzumab= $(0,1,0)(0,0,1)_4$; IV originator = (0,1,0); SC= (0,1,0); Total claims = $(2,1,0)(2,0,0)_4$; Number of patients = $(3,1,0)(1,0,0)_4$
- † SC formulation was introduced in Q4 2014; the first biosimilar was introduced in Q3 2017.
- ‡ SC trastuzumab was available from Q4 2014 to Q2 2020.
- * p < 0.05, ** p < 0.01, *** p < 0.001
- Abbreviation: SC = Subcutaneous; IV = Intravenous

**Table 2.** Segmented regression estimates of quarterly changes in trastuzumab expenditure following the introduction of subcutaneous (SC) formulation and intravenous (IV) biosimilar entry

| Segmented Term | Trastuzumab sales value (log-transformed) | | | | Patient-level healthcare expenditure | |
|---|---|---|---|---|---|---|
| | Total | IV | IV originator | SC‡ | Total | Breast-cancer related |
| Slope before intervention | 0.035** | 0.034 | 0.037* | 0.640*** | 0.012*** | 0.0127*** |
| **Introduction of SC Trastuzumab†** | | | | | | |
| Step change after intervention | -0.004 | 0.071 | 0.138 | - | -0.022 | -0.018 |
| Slope change after intervention | -0.046*** | -0.134*** | -0.142*** | - | -0.003 | -0.003 |
| **Introduction of Trastuzumab biosimilar†** | | | | | | |
| Step change after intervention | -0.159*** | -0.167* | 0.0004 | 0.055 | 0.043* | 0.003** |
| Slope change after intervention | 0.032*** | 0.131*** | 0.058*** | -0.822** | 0.011*** | 0.014*** |

- ARIMA specification: Total trastuzumab = (3,0,0); IV Trastuzumab= $(0,1,0)(2,0,0)_4$; IV originator = $(2,1,3)(1,0,0)_4$; SC= $(2,0,0)(2,0,0)_4$; Total healthcare cost = $(2,0,0)(1,0,0)_4$; Breast cancer related healthcare cost = $(2,0,0)(1,0,0)_4$
- † SC introduction occurred in 2014Q4; first biosimilar introduced in 2017Q3.
- ‡ SC Trastuzumab was available from Q4 2014 to Q2 2020.
- * p < 0.05, ** p < 0.01, *** p < 0.001
- Abbreviation: SC = Subcutaneous; IV = Intravenous

## Conclusions

- SC reformulation created new market segments and increased utilization, whereas biosimilars competed within existing IV markets with limited impact.
- Without demand-side policies complementing South Korea's price-linking approach, biosimilar cost-saving potential remains constrained by evergreening strategies.
- Balanced policies supporting both innovation and sustainable competition are essential.

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