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Similar Products at Different Prices: Can Biopharmaceutical Companies Segment Markets?

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ABSTRACT *New data on Medicare Part B payments show provider-level utilization of two similar but distinct biologic medications used to treat wet age-related macular degeneration. Their interaction provides insight into the ability of manufacturers to effectively segment markets and suggests some analogies for the future interplay between originator biologics and biosimilars. In particular, most ophthalmologists administer a mix of Avastin (used off-label), Lucentis, and other drugs; only a small share exclusively choose Lucentis. This is inconsistent with the hypotheses that (1) the manufacturer is able to effectively segment the market, and (2) the major factor driving physicians' product choice is the financial motivation. The data are consistent with the notion that physicians typically exercise medical judgment on a patient-by-patient basis and that product choice is driven largely by factors other than simple financial interests. This raises important dynamic efficiency considerations regarding incentives for future biologic competition.*

Key Words: Pricing; Biotechnology; Physician; Prescription; Firm Behavior.

JEL classifications: L110, D4, L650, I11, L2.

Background

The biopharmaceutical industry has been studied extensively by scholars in industrial organization and public policy because its structure, regulatory environment, and pricing are unique among modern industries. Early articles exploring the dynamics of this industry include Comanor (1964, 1986).

Among the most fundamental aspects of the modern biopharmaceutical industry are the discovery and development of new medicines and the interplay between alternative treatments. In the most common case, when a

The following product names referenced throughout the article are registered trademarks of the indicated companies: Lucentis, Genentech, Inc.; Avastin, Genentech, Inc.; Eylea, Regeneron Pharmaceuticals, Inc.; Visudyne, Novartis, AG; Macugen, Eyetech, Inc.

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new therapy is introduced, that therapy typically enjoys patent protection (or in some cases another form of regulatory exclusivity) from immediate copying for some period, during which it may compete with previously developed alternative (nonchemically identical) therapies. After patent protection (or regulatory exclusivity) ends, small-molecule branded drugs are subject to intense competition. This competition comes from generic entrants who face low manufacturing costs, typically charge far lower prices, and take advantage of institutional pressures that encourage the use of generics. Key early contributions to the literature on the effects of patent expiration and the impact of generic entry are Caves et al. (1991) and Grabowski and Vernon (1992).

An interesting development currently unfolding in the United States – one that has been unfolding in Europe for nearly a decade – is the competitive interplay between innovative large-molecule biologic medications and their “generic” counterparts, or “biosimilars.” A regulatory pathway for the review of biosimilars was authorized under the Biologics Price Competition and Innovation Act of 2009 (BPCIA; part of the Affordable Care Act), but the exact details of what it takes to gain Food and Drug Administration (FDA) marketing authorization are still evolving. An important step in that process, however, is an FDA review committee’s recommendation for approval of the first biosimilar in the United States (see Novartis 2015). Going forward, the interplay between competing similar but distinct biologic medications will be an issue of intense interest for policy makers, biopharmaceutical company management, patients, and academics.

There is a substantial literature that attempts to forecast how competition will unfold between originator biologics and the biosimilars that reference them. The primary view is that the competition confronting originator biologics from biosimilars will bear only faint similarities to the brand-generic experience. A partial list of articles discussing the potential outcome of biosimilar entry includes the following: Grabowski, Guha, and Salgado (2014); Trusheim, Aitken, and Berndt (2010); US Federal Trade Commission (2009); Grabowski and Kyle (2007); Grabowski, Ridley, and Schulman (2007); and Trusheim, Berndt, and Douglas (2007).

We may not see the equivalent of the patent cliff that occurs in the small-molecule sector for three reasons: (1) the manufacturing of biologics is far more complex and costly than the manufacturing of small-molecule drugs; (2) the regulatory approval process is and will likely remain far more involved, keeping the number of potential competitors down; and (3) physicians and patients may not be quick to adopt unproven biosimilars. Meaningful utilization of originator molecules is likely to persist beyond patent (or data exclusivity) expiration, and prices may not fall dramatically over short periods of time. Over the coming years, as biologic therapies come to play an increasingly important role in medical care, the industrial organization of the biopharmaceutical industry is likely to change as well. It is useful to look into current market dynamics to get a sense of the direction and degree of those changes.

As suggested above, an important question will be what happens when two similar but distinct medications can be substituted for each other in a high-value medical application. Although, as indicated, biosimilar entry in the United States is only on the verge of becoming a reality, there are examples of competition between different branded versions of biologics employing similar mechanisms of action, and these can shed light on the important dynamics that will unfold.

Here, we focus on one particular example of the interplay between similar biologic therapies that are used for the prevention of blindness as a result of wet age-related macular degeneration (AMD). These products are Genentech's Lucentis and Avastin. The chemical names of Avastin and Lucentis are, respectively, bevacizumab and ranibizumab. The brand names will be used for ease of discussion.

Avastin was approved by the FDA in February 2004 with an indication for the treatment, in combination with certain chemotherapy agents, of metastatic colon and rectal cancer. It has since been approved for treatment of a wider range of cancers. Lucentis received FDA approval in June 2006 to treat wet AMD and has also received FDA approval for two additional indications, but our focus here will be on wet AMD treatment.

Following the early emergence of evidence that Avastin injections might be beneficial in the treatment of wet AMD, ophthalmologists began using Avastin for this unapproved (off-label) use. There is clinical trial evidence suggesting that patients receiving Lucentis and Avastin for AMD have comparable outcomes (US National Institutes of Health 2012), but the FDA has also issued an alert to healthcare professionals indicating concern about potential safety risk from using inappropriately repackaged use of Avastin in its off-label use in treating wet AMD (US Food and Drug Administration 2011a).

While the price per treatment of Avastin in its approved use (cancer) is not terribly different from the price of Lucentis in its approved use (wet AMD), the quantities needed in each use differ dramatically. For example, the dose of Avastin used in clinical trials for cancer is 500 times the dose used to treat wet AMD (US National Institutes of Health 2012). As a result of the dramatically different demand structures for these two drugs, the off-label use of Avastin to treat wet AMD results in much lower expenditures (see, e.g., Pershing et al. 2015). Lucentis sells for about \$2,000 per injection, while the dose of Avastin typically administered by ophthalmologists for the treatment of wet AMD sells for approximately \$50 per injection (see Whoriskey and Keating 2013). Hence, it may be in the manufacturer's economic interest to attempt to separate the markets for Lucentis and Avastin in their respective approved uses.

A key question in the industrial organization of the biopharmaceutical industry is whether the owner of two apparently substitutable products with two distinct uses is able to segregate markets and sustain different prices that correspond to the value of the products in those distinct uses. While it might seem obvious that in an open market, price sensitive buyers would select the lower-priced product that suits their needs, there are questions about how patients and physicians perceive and respond to products that may or may not seem identical. There are also issues of dynamic efficiency and the incentive to develop new therapies. If a prospective innovator is unable to earn financial rewards for developing products that provide valuable treatment for serious conditions, less than optimal investment will be called into the search for such innovations. The appropriate balance between the static efficiency gains associated with allowing physicians and patients to choose Avastin for wet AMD treatment and the dynamic efficiency gains associated with the development of new treatments is an important question that is beyond the scope of this article, but it deserves careful attention as the market for biosimilars evolves.

Another important question is the degree to which biopharmaceutical manufacturers are able to determine the conditions of use of their products.

Clearly, if manufacturers attempted and were able to exert substantial influence in cases such as this, one would expect to observe substantial use of the higher-priced Lucentis and minimal use of the lower-priced alternative. A recent change in Medicare policy provides some insight into the utilization patterns of these two products for the treatment of wet AMD. What we find is that despite economic incentives to segment the market for these two products, the market is in fact not segregated very completely. As indicated in recently released Medicare Part B data, a large share of the potential demand for wet AMD treatment is filled with Avastin. In addition, the physician-level patterns of use between these two products are consistent with conditions that might reasonably be expected if physicians are acting in their patients' interests.

Insight from a New Data Source

Lucentis versus Avastin

Recently, the Centers for Medicare and Medicaid Services made available to the public for the first time detailed data regarding the Medicare Part B program. The data cover all of 2012 and contain a wealth of information – more than nine million records of data for more than 880,000 healthcare providers. For the first time, one can look up a participating physician by name in a publicly available data set and observe a great deal of information, including the services provided, the drugs administered, and the amounts paid by the Medicare Part B program for those services and drugs. Medicare Part B covers doctors' services and outpatient care (US Centers for Medicare and Medicaid Services 2012). A brief article discussing the reaction to this data release and the issues discussed here was recently published in the online magazine *Pharmaceutical Executive* (2014) by three of our co-authors, Scher, Twigg and Huson.

The choice physicians make between Lucentis and Avastin has been a common topic in the health policy literature (see, e.g., Hutton et al. 2014). The release of the Medicare data attracted a great deal of attention in the popular press, with prominent articles appearing in many of the country's most widely read newspapers, websites, and other periodicals (see, e.g., Abelson and Cohen 2014; Chen and Pearson 2014; Luhby 2014). Many of these articles focused on high-billing physicians, highlighting the amounts they have been paid by Medicare, and in some cases questioning the medical practices in which these physicians have engaged. Ophthalmologists specifically received scrutiny as a result of the data's public release; several articles in the press identified these physicians as frequent high billers.

Several articles focused on ophthalmologists' prescribing behavior with respect to Avastin and Lucentis for the treatment of wet AMD. Medicare Part B payment to doctors when they inject these drugs is set at a 6% markup over the drug's Average Sales Price (ASP), and hence doctors receive higher Medicare payments when they use a drug that costs more to acquire.

The difference in the Medicare Part B payment between these two products has been cited in articles to suggest that financial incentives may be motivating ophthalmologists to use Lucentis instead of Avastin. Of course, one needs to be cautious about what inferences can and cannot be drawn based on these data alone – for example, the data do not provide information on the reasons for the physician's product choice, the severity of patients' medical conditions,

or patient outcomes. Also, the public data do not contain claim-level information that would provide additional insight. Despite these limitations, these new data are useful in providing preliminary insight into two competing hypotheses regarding doctors' use of these drugs.

- Do ophthalmologists who administer Lucentis appear to be doing so primarily because they earn higher Medicare payments? Specifically, if doctors view Lucentis and Avastin as very similar or identical, and if the only factor affecting the decision to administer one versus the other is whether the doctor is driven by financial incentives (and hence inclined to use Lucentis) or cost sensitivity (and hence inclined to use Avastin), then one would expect doctors to administer one or the other but not both.
- Alternatively, do ophthalmologists who administer Lucentis appear to be doing so because they are exercising medical judgment on a patient-by-patient basis? Specifically, if doctors view Lucentis and Avastin as at least somewhat differentiated, then they may believe that Lucentis is better for some patients and Avastin is better for others. In this case, one would expect doctors to administer a mix of the two drugs to their patients, depending on patient need.

To gain insight into these competing hypotheses, we focused on ophthalmologists who used these drugs frequently, because these physicians had a greater incentive to choose the higher-priced product. Specifically, we limited the data to ophthalmologists with 200 or more patients who received injections of these drugs over the course of 2012. A total of 547 ophthalmologists met these criteria and were included in our analysis. Among these high-volume doctors, 11% administered only Avastin to their patients, 19% administered only Lucentis, and 70% administered a mix of the two drugs – Avastin to some patients and Lucentis to others. Note that we obtained similar results when limiting our analysis to ophthalmologists with 100 or more patients. In particular, 18% administered only Avastin to their patients, 24% administered only Lucentis, and 59% administered a mix of the two drugs to their patients. In total, Avastin and Lucentis use was split quite evenly between the two products; in this sample, if all Avastin use had been switched to Lucentis, Lucentis use would have increased by 97%. This pattern of mixed utilization is consistent with the hypothesis that the vast majority of these high-prescribing doctors used Avastin on some patients and Lucentis on others, and it suggests that they were exercising medical judgment in their choice of treatment on a patient-by-patient basis, not simply responding to economic incentives.

Moreover, it is obvious from even this simple analysis that if the manufacturer attempted to and was successful in separating the market for Lucentis from Avastin, utilization of Lucentis would be much more common, perhaps universal relative to Avastin in treating wet AMD. This is clearly not the case. In fact, slightly more patients treated by ophthalmologists are treated with Avastin than are treated with Lucentis. Given the price difference between the two products, if all physicians in this group who use Avastin switched entirely to Lucentis, revenue to the manufacturer from this sample of physicians would nearly double. Obviously, other elements are exerting substantial influence on product choice.

For doctors who used these products in high volumes, the “mix” group often included a substantial number of patients being treated with each of the products. That is, the mix group was not driven by doctors who used one drug on nearly all of their patients and the other on a small fraction. In Figure 1, we illustrate the number of patients treated with Lucentis as a fraction of the total number of patients treated with either Lucentis or Avastin for each of the high-volume doctors. Specifically, each data point represents one of 547 high-volume doctors, and the graph measures each doctor’s Lucentis “patient share.”

As shown in Figure 1, many high-volume doctors administered a substantial amount of both products. For instance, the shaded region shows that many of these doctors did not concentrate >80% of their patients on one drug but rather used both drugs in significant shares. This shaded region amounts to >40% of the high-volume ophthalmologists. We obtain similar results when analyzing the proportion of treatments as opposed to the proportion of patients.

This analysis thus casts some doubt on the hypothesis that many high-volume doctors are administering Lucentis primarily because they are motivated by profits, and the analysis lends some support to the hypothesis that doctors are exercising medical judgment in their choice of treatment or other factors are influencing product choice.

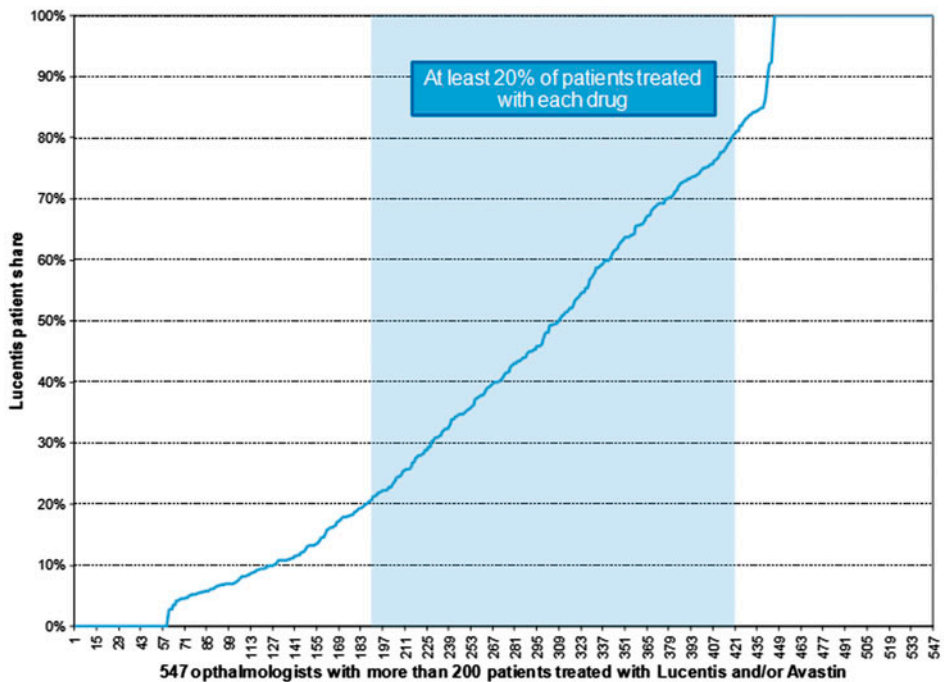


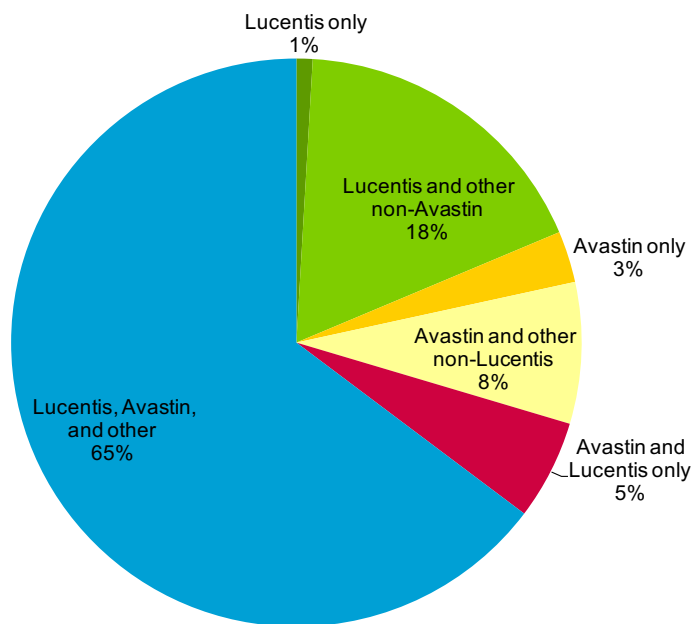
Figure 1. Breakdown of Lucentis patient share for high-volume ophthalmologists.

Interaction with Other Treatments

Although much attention has been paid to the interplay between Lucentis and Avastin, several other drugs are also used to treat wet AMD. These include Visudyne, Macugen, Eylea, and Triamcinolone (which is not approved to treat wet AMD but is sometimes used off label to do so). Lucentis, Avastin, Macugen, and Eylea are administered as stand-alone injections. Visudyne is administered in conjunction with photodynamic therapy. Triamcinolone can be administered as a stand-alone treatment or in combination with one of the aforementioned drugs (see Gopal and Sharma 2007; Mayo Clinic 2014). Accounting for these alternatives in the analyses described above offers several additional interesting insights.

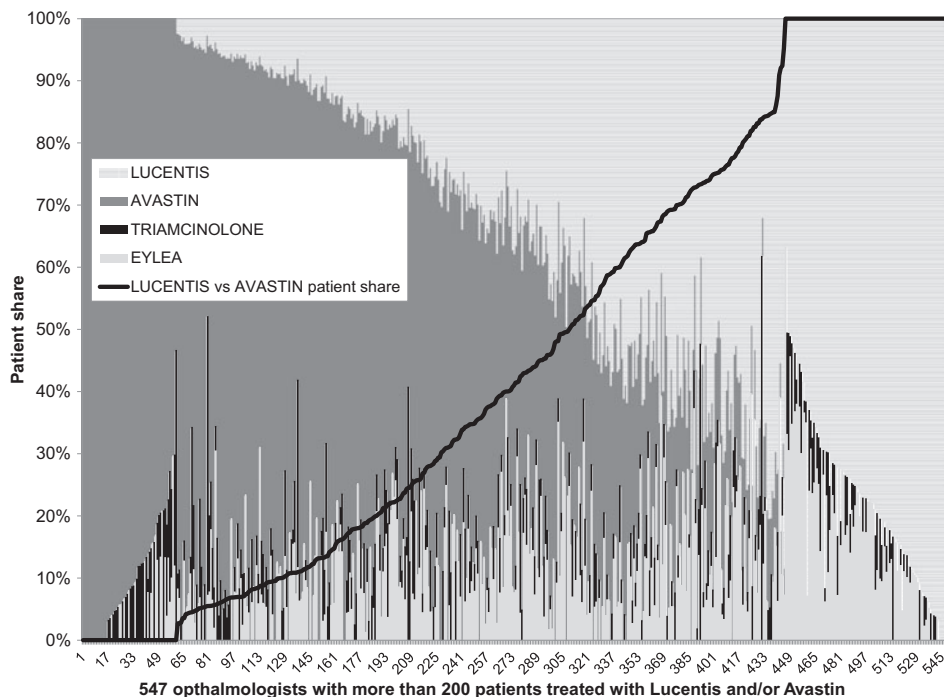
First, after accounting for these drugs, very few doctors remain in the Lucentis-only category. In particular, as shown in Figure 2, only five (or <1%) of the 547 high-volume doctors prescribe only Lucentis. This suggests that very few physicians prescribe in a manner consistent with a solely profit-motivated orientation and that any efforts by the manufacturer to encourage exclusive use of Lucentis, as the first product approved for the treatment of this important disease, are relatively ineffective. These data suggest a very competitive set of interactions between alternative therapies. Note that ophthalmologists may use some of these drugs for conditions other than wet AMD, but the available data do not allow us to distinguish particular uses.

Figure 3 provides a more granular look at the prescribing patterns of these doctors. Figure 3 expands Figure 1 to include Eylea and Triamcinolone as well



Note: "Other" includes Visudyne, Macugen, Eylea, and Triamcinolone.

Figure 2. Breakdown of wet age-related macular degeneration (AMD) treatments for ophthalmologists with 200 or more patients treated with Lucentis and/or Avastin.



Note: For illustrative purposes, this chart does not show Visudyne and Macugen, which account for a very small patient share.

Figure 3. Share of wet AMD drug treatments for high-volume ophthalmologists.

as Lucentis and Avastin. Specifically, each data point represents one of 547 high-volume doctors, and the graph measures each doctor's "patient share" for each of the drugs.

Figure 3 illustrates that many of the doctors who were characterized as Avastin-only in Figure 1 actually administered other wet AMD drugs to a substantial number of their patients. Most notably, the chart shows that a sizeable share of these doctors' patients received Triamcinolone. As mentioned above, Triamcinolone is used off label to treat wet AMD and is also relatively inexpensive, costing less than \$20 for a 2–4 mg dose.

Figure 3 also reveals that the doctors who were characterized as Lucentis-only in Figure 1 administered other wet AMD drugs to a substantial number of their patients. In particular, the graph shows that these doctors administered Eylea to a sizeable share of their patients, though clearly to fewer than they administered Lucentis. Eylea was approved in November 2011 and has been shown to help when patients do not respond to Lucentis or Avastin (see Bakall et al. 2013; US Food and Drug Administration 2011b). The drug is relatively expensive (approximately \$1,850 per dose), but it only needs to be injected half as frequently as Lucentis and Avastin (see American Macular Degeneration Foundation 2014).

Taken together, these observations have various potential explanations. First, one could interpret them as suggesting that certain doctors are more

inclined to use off-label treatments, and hence doctors who tend to use Avastin over Lucentis also tend to use Triamcinolone relatively frequently. Second, because Avastin and Triamcinolone are relatively inexpensive, these observations could suggest that certain doctors choose less expensive products for their patients while others choose more expensive products, such as Lucentis and Eylea. This explanation, however, could also be consistent with various motivations. For instance, it could be the case that the doctors who use Lucentis and Eylea frequently have more complex patients or believe that these on-label products are better for patients than the off-label alternatives (Avastin and Triamcinolone). Although the data do not allow a fine distinction among the competing hypotheses, two key observations arise:

- Very few doctors (<1% as shown in Figure 2) administered only what was likely to be the most profitable product to them. If financial incentives dominated among this group of physicians, one would expect a much larger share of them to have prescribed the most expensive product.
- Doctors who more often administered Lucentis also provided certain services that were used to diagnose and track the progression of wet AMD and other eye conditions more frequently. For example, in our sample, the number of claims a doctor submitted for each of the following services is positively correlated with the number of Lucentis claims the provider submitted: optical coherence tomography (CPT code 92134), fluorescein angiography (CPT code 92235), ICG angiography (CPT code 92240), and fundus photography (CPT code 92250). Optical coherence tomography (CPT code 92134) uses special rays of light to scan and produce an image of the retina that shows whether the macula is thickened or abnormal and whether fluid has leaked into the retina. Fluorescein angiography (CPT code 92235) involves injecting fluorescein dye into a vein and then taking pictures by using a special camera to see if any of the dye has leaked from the blood vessels behind the macula. ICG angiography (CPT code 92240) is similar to fluorescein angiography but uses a different dye that highlights different problems in the eye. Fundus photography (CPT code 92250) uses a special camera to take three-dimensional color images of the macula in order to see damage to different layers of the retina. In 2012, the Medicare physician fee schedule rates for CPT codes 92134, 92235, 92240, and 92250 were \$44.93, \$137.17, \$248.47, and \$76.58, respectively (National Health Service 2014). The relevant correlation coefficients are 0.42, 0.26, 0.37, and 0.20, respectively, all of which are statistically significant at the 1% level. This suggests that doctors who administered Lucentis had a more complex patient population with more severe conditions. Alternatively, it could indicate that these doctors provided more in-depth patient care.

One other observation regarding these doctors merits noting. Those who prescribed Lucentis more often relative to Avastin tended to be located in counties with higher per-capita income than those who prescribed Avastin more often. (Per capita income was taken from the 2012 American Community Survey administered by the US Census Bureau.) While this relationship is not particularly strong, the correlation coefficient between a doctor's Lucentis patient share and per-capita income in the doctor's county is 0.24, and is

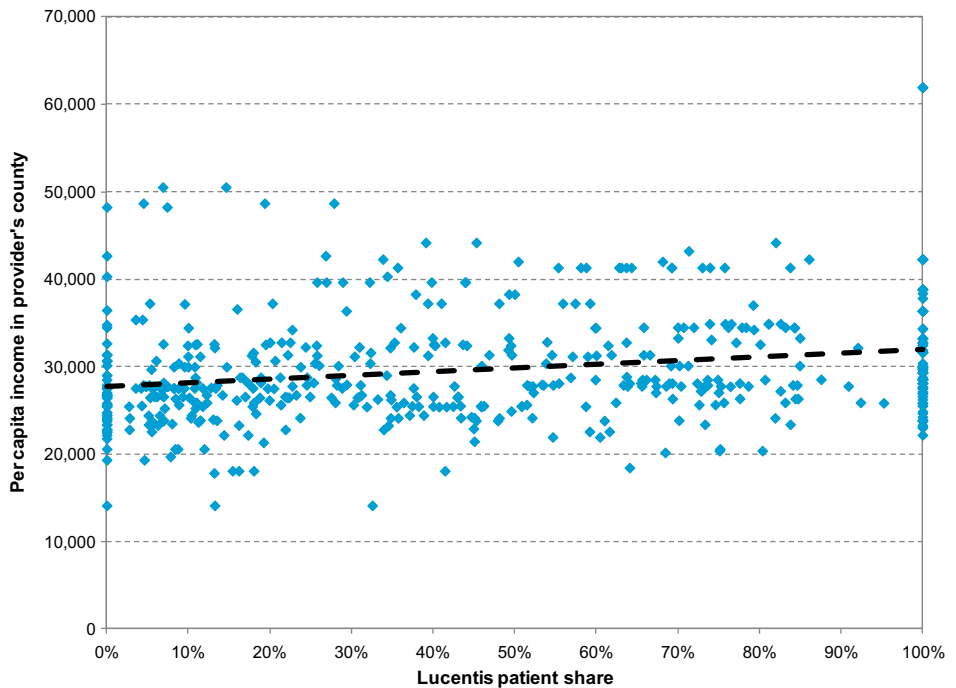


Figure 4. Relationship between Lucentis patient share and per capita income in provider's county for high-volume ophthalmologists.

statistically significant at the 1% level. The relationship between income and Lucentis share is illustrated in Figure 4.

Obviously, this correlation is modest, and variation around the trend is substantial. Of course, it would be far preferable to estimate the effect of patient income on therapy choice in the context of a regression framework that corrected for other individual and prescriber characteristics, but the data on individual patient and physician characteristics necessary for such an examination are not readily available. Nevertheless, physicians practicing in higher-income areas are likely to have patient populations that would be somewhat less sensitive to differences in out-of-pocket cost or who may view any therapeutic differences between the products as more important when the outcome involves retaining or losing vision. It is important to note that the majority of Medicare Part B beneficiaries have supplemental insurance that covers some or all of their coinsurance, so in many cases the patients are not likely to foot much if any of the bill (see Jacobson, Huang, and Neuman 2014).

Conclusion

In summary, the newly released data on Medicare Part B payments suggest that many doctors chose Avastin for some patients and Lucentis for others, and the data show most clearly that only a very small share of doctors exclusively chose Lucentis. Accounting for a broader set of drugs that can be used to treat wet AMD – Lucentis and Avastin, as well as Visudyne, Macugen,

Eylea, and Triamcinolone – reveals that the vast majority of doctors administered multiple drugs to treat wet AMD. This is inconsistent with the hypothesis that the major factor driving product choice between these two products is a simple financial motivation on the part of the physician or the manufacturer.

Rather, it is consistent with the notion that physicians typically exercise medical judgment or are responsive to other factors on a patient-by-patient basis. Moreover, and perhaps most interestingly from the perspective of the industrial organization of the biopharmaceutical industry, and for public policy discussions, it seems quite clear that there are limitations to manufacturers' ability to segment markets.

Furthermore, accounting for a broader set of drugs that can be used to treat wet AMD – Lucentis and Avastin, as well as Visudyne, Macugen, Eylea, and Triamcinolone – reveals that the vast majority of doctors administered multiple drugs to treat wet AMD. The physicians who were most likely to use Lucentis also tended to be those who most likely used the newer biologic therapy, Eylea, which is primarily indicated for patients who do not have satisfactory results on initial therapy. This may suggest that patients treated by such doctors have more complicated medical conditions or are for some unobserved reason more likely to respond better to products specifically indicated for the condition. Finally, physicians who administered Lucentis more often also performed more eye-imaging procedures to diagnose and track the progression of wet AMD and other eye conditions. This suggests that such patients may indeed be more medically complex and that they may be patients for whom the FDA-approved therapy may be deemed to be more appropriate by the physician, the patient, or both. All these patterns lend support to the notion that therapy choice is driven by patient-specific characteristics, but these patterns also merit further investigation with more detailed data than we have available.

In terms of the future of biosimilars and the industrial organization of the biopharmaceutical sector, three preliminary observations seem obvious.

- (1) Similar but not identical goods can coexist, filling a similar need despite substantial price differences. This illustrates the relative inability of the manufacturer to segment the market and drive sales toward the higher-priced product.
- (2) Related to the first point, these data suggest that physicians are making choices based on factors other than economic impact. Though the available data do not allow one to identify the physician's motivation, they do suggest that perhaps absent a specific regulatory designation of interchangeability, higher-priced innovators may be able to maintain meaningful share in the presence of low-priced comparators.
- (3) Finally, there are important dynamic efficiency considerations that need to be taken into account in thinking about the market for products such as Avastin and Lucentis. These considerations will apply as the biosimilars market unfolds. The former product was introduced first and represented an important breakthrough in oncology. The second product was also a substantial breakthrough in treating a serious condition leading to blindness. The R&D and regulatory review and approval process for new therapies is long, costly, and uncertain. There

are meaningful questions about whether – given the evident inability of the manufacturer to effectively separate the demand for two patent-protected products – a prospective innovator in a similar setting would be able to justify the investment into the development of the latter product. Indeed, half a loaf may be sufficient to call forth the economically appropriate level of innovation in such settings, but given recent trends in the industry, that is not as obvious as it may seem (Berndt et al. 2015). This and the other issues raised by this article are matters that merit continuing investigation and discussion by economists and policy makers alike.

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