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Does the Identity of the Third-Party Payer Matters for Prescribing Doctors?

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Does the Identity of the Third-Party Payer Matters for Prescribing Doctors?[1]

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Abstract

TNF-alpha inhibitors represent one of the most important areas of biopharmaceuticals by sales, with three blockbusters accounting for 8 per cent of total pharmaceutical sale in Norway. Novelty of the paper is to examine, with the use of a unique natural policy experiment in Norway, to what extent the price responsiveness of prescription choices is affected when the identity of the third-party payer changes. The three dominating drugs in this market, Enbrel, Remicade, and Humira, are substitutes, but have had different and varying funding schemes - hospitals and the national insurance plan. A stochastic structural model for the three drugs, covering demand and price setting, is estimated in a joint maximum likelihood approach. We find that doctors are more responsive when the costs are covered by the hospitals compared to when costs are covered by national insurance.

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1. Introduction

The agency problem faced by insurance companies and governments, and its consequences for health care financing has been subjected to extensive theoretical and empirical research[2]. The moral hazard problem in health care arises due to third-party funding and doctors' superior information about diagnosis and preferred treatment choices. In an insurance-based health care system there are at least two candidates for being the third-party payer. When prescribing a drug on behalf of an insured patient, the cost may be covered by traditional insurance plans – private or public – on a fee-for-service basis - or by the hospital with which the doctor and patient are affiliated. The agency problem differs between a global hospital funding scheme and a fee-for-service approach adopted by traditional insurance plans. Treatment costs covered by the national insurance plan do not represent a direct cost for the doctor and the hospital. To the extent that treatment costs still affect the choice of drug under a pure national insurance plan funding can be explained by doctors' understanding and adherence to national guidelines for cost-effective treatment choices. However, when treatment costs are covered by the hospital, the opportunity costs becomes more "tangible" to the doctors. Increased treatment costs on one patient reduce available resources for other activities at the affiliated hospital. For this reason, treatment choices may be under a tighter control or monitoring when costs are covered by the local hospital instead of a national, and tax funded, insurance plan.

With use of a unique natural policy experiment in Norway, we are able to investigate to what extent the price responsiveness of prescription choices is affected when the identity of the third-party payer changes. Our case in point is the Norwegian market for Tumor Necrosis Factor (TNF) alpha inhibitors[3].

When the market for TNF-inhibitors opened in Norway in 2000, the first entrant *Enbrel* was fully covered by the obligatory national insurance plan. The treatment with

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[2] See McGuire (2000) for a review

[3] To date TNF-alpha inhibitors represent the most important way to treat arthritis and other autoimmune diseases (Feldmann and Maini, 2003).

Enbrel is initiated by the hospital doctor, but the cost was automatically covered by the national insurance plan. The second entrant *Remicade* did not obtain the same type of coverage. Instead the treatment cost had to be fully covered by the doctor's affiliated hospital. Importantly, the hospitals' budget did not include earmarked grants for these patients. Cost of treatment with Remicade, therefore, competed with other expenses within the hospital. This sharp asymmetry in funding scheme reflects a quality attribute of the two drugs. Enbrel is administrated by the patients themselves (pump injections), while Remicade requires several hours infusion at hospitals. In fall 2002 the government modified the plan for Remicade. The government required a copayment of 20 per cent from the doctor's affiliated hospital. Enbrel maintained its full insurance plan coverage. The third entrant *Humira* is also administrated by pump injections by patients, and received the same funding plan as Enbrel when the drug entered in January 2003.

The important policy change exploited in our study, however, took place in 2006. Then the asymmetry of financing between Enbrel and Humira, and Remicade was entirely removed by returning the entire funding responsibility to the hospitals for all three drugs. Since then all costs of treatment with TNF-alpha inhibitors have to be covered by the doctors' affiliated hospital. By creating large and exogenous variations in hospital and insurance plan treatment costs, these funding switches becomes the crucial source of identification in our empirical model.

To investigate how the different funding plans affected price responses among doctors, we have specified a discrete choice model in which the doctor's choice of TNF-alpha inhibitors depends on the prices and the funding schemes. The discrete choice model results in three market share equations (the aggregates of multinomial logit probabilities) which are estimated on aggregate time series. The results show that doctors' choice of TNF-alpha inhibitor is responsive to price differences, and that this price response becomes stronger when hospitals cover the costs.

However, when the squared residuals from the baseline model are regressed against prices we obtain significant results, which imply that homoscedasticity is rejected. The explanation for this could be that there are unobserved factors such as quality aspects, which are absorbed in the random terms and correlate with the prices. To deal with this problem we have estimated jointly the market share and price-setting

equations, assuming monopolistic competition. We allow for correlations in unobserved variables affecting both demand and prices. Now, homoscedasticity in the demand function is not rejected. The result that doctors appears to be more price-responsive when the costs are covered by the hospitals compared to when costs are covered by national insurance becomes more significant. As expected, the numerical values of the own price elasticities increase when quality aspects are accounted for (the market model) compared to when they are not (the demand model only).

Another interesting result emerges due to the estimated correlation structure of the model. The correlation between the unobserved factors in the market share of Remicade (the less expensive an less efficient treatment) and price setting is estimated to be significantly negative. This implies that if there is negative shock in the price of Remicade, then its market share increases, cet.par. Due to the observed part of the price setting in the monopolistic competition model the producer of Enbrel (and also of Humira) respond by cutting prices. However, in the model we allow for correlation between the unobserved factors in the price-setting of Enbrel (the more expensive and more efficient treatment) and Remicade. The correlation is estimated to be significantly negative. This negative correlation between the unobserved factors in the pricesetting of Enbrel and Remicade therefore modifies the price response due to the observed part of price-setting and is obviously due to unobserved quality characteristc across the two drugs. The better quality of Enbrel makes it possible to reduce the price less as a response to a negative shift in the price of Remicade. This lesser response is here captured by the probabilistic structure of the price-setting part of the model.

The reminder of the paper is organized as follows. In Section 2 we relate our paper to the existing literature. Section 3 presents the econometric model and Section 4 presents the data. Section 5 gives the results and Section 6 concludes.

2. Related literature

Our research relates to two strands of the health economics literature. One is the literature on pharmaceutical demand and price elasticities. The other is the literature studying the effect of reimbursement schemes on spending. However, these two areas of research are interlinked since many of the studies of price responses in pharmaceutical demand exploit

variations in reimbursement schemes and patient charges.

Ellison et al. (1997) estimate a demand model for a class of anti-infective drugs called cephalosporins. Their data contains four different chemical substances, and three of these substances experienced significant generic entry in the sample period. In the case of substitution between different substances (therapeutic substitution), they find evidence of low (and often insignificant) price responses in demand. Price responses are stronger when the choice is between brand-name and generics (generic substitution). One of the drugs comes out with a significant own-price elasticity of -0.3. Cephalosporin drugs differ from our TNF-alpha inhibitors by having a relatively low level of hospital consumption.

Berndt et al. (2003) estimate a demand model for a growing market with competing brand-names available. They use data for H2-antagonist antiulcer, and their data starts at the entry of the first patent (Tagament). Similar to our study, therefore, they investigate the pharmaceutical demand in a market with several competing brand-name (patented) drugs. They develop a rich model that includes a dynamic component of diffusion. Their market share model allows the drug choice to depend on prices, in addition to marketing. Doctors' are found to respond to prices, but similar to the findings of Ellison et al. (1997), price responses appear to be relatively low. They find own-price elasticities in the range of about -0.3 and -0.6.

There is a larger literature studying the demand responses to changes in co-payment by patients. A seminal contribution was made by Leibowitz et al. (1985), who used data from the Rand Health Insurance experiment to study the relationship between the degree of cost sharing with patients and prescription drug utilization. They found that patients with a more generous insurance scheme buy more prescription drugs. Another early contribution, using monthly time-series from the National Health Service (NHS) in England, is O'Brien (1989). He found co-payment elasticities in the range of about -0.3 and -0.6. A more recent contribution along this line of research is made by Contoyannis et al. (2005). Using micro data (individual patients) from Quebec, they estimate the elasticity of expenditure for prescription drugs with respect to patients' marginal prices (cost sharing). These were found to be relatively low - in the interval -0.12 to -0.16.

Iizuka (2007) is a recent contribution to the literature on agency problems in the prescription drug market. In the Japanese market, doctors make profit from selling prescribed drugs. Using data with both prices and doctors' own mark-up, he estimates a nested logit demand model for the hypertension market, including 40 brands in 5 different therapeutic classes. Iizuka finds that prescription decisions are influenced by the size of mark-up, but that doctors care more about patient welfare than their own profit. Hence, if the retail price of a brand increases, the doctor becomes less likely to prescribe that drug. Other papers studying the importance of doctor and prices in prescription choices are Coscelli (2000) and Lundin (2000). The latter study relates to our analysis by showing that doctors' responses to prices are influenced by the funding source. In Lundin's analysis the two funding sources are the patients themselves or the insurance provider. The main contribution of Lundin is to show how the level of patients' co-payment influences doctors choices (between generics and brand-name). He finds that doctors' are more responsive to patients' co-payment than the cost of the insurance provider.

Hellerstein (1998) provides evidence of the importance of insurance plans for the agency problem in prescription choices. She finds that doctors with a higher fraction HMO-patients (Health Maintenance Organization) relative to patients who are enrolled in traditional insurance plans, more often prescribe generics instead of the brand-name drug. Because her data did not contain prices, she is not able to study price responsiveness.

3. Econometric models.

The decision-making unit on the demand side is the physician, who acts as the patient's agent (Arrow, 1963). Therefore, decision-making-units (DMU) are here represented by physician-patient couples, $i=1,..N_t$.

The model is derived from a random utility model (see Train, 2009 for an overview of such models) in which DMUs chooses among the available drugs, $j=1,...,J$, to maximize utility.

The number of drugs is three. To this end they are numbered: Enbrel no1, Humira no2 and Remicade no3. The number of periods is 62.

Utility for the decision-making unit is given by

(1) $U_{ijt} = -v_{jt}p_{jt} + a_{jt} + \varepsilon_{ijt}; i=1,2,,,N_t; \quad j=1,2,3; t=1,2,,,62$

where a_{jt} is an indicator of perceived treatment quality of drug j at time t. This is a common quality-indicator that applies to all patients that can benefit from TNF-alpha therapy. Like in Berry et al (1995) we will assume that a_{jt} depends on observed as well as unobserved attributes, which will be specified below. The unobserved part may reflect quality attributes of the three drugs that could be priced out in the market and hence the unobserved parts may correlate with prices. This creates estimation problems that will be addressed below. p_{jt} is the price variable associated with drug j at time t and v_{jt} are coefficients that capture the impact of the costs of treatment on utility. We have specified the price part of the utility function so that a negative impact of price on utility requires v_{jt} to be positive. The random variable ε_{ijt} is iid extreme value.

The costs of treatment with TNF-alpha inhibitors are covered by a third-party. There are two third-party payers. One is the National Insurance Plan (NIS) (termed "I"), and the other is the hospital with which the prescribing doctor is affiliated (termed "H"). The funding split between the insurance plan and the hospital varies over time and across drugs: At a given time t the drug costs are fully paid by the hospital, fully covered by the insurance plan, or split between the two with 80 percent covered by insurance and 20 percent by hospitals.

Thus, v_{jt} is given by:

(2) $\quad v_{jt} = \alpha_{Ijt}\beta_I + \alpha_{Hjt}\beta_H \, ; j=1,2,3$

where

(3) $\quad \begin{aligned} \alpha_{Ijt} &= \{1, \quad 0.8, \quad 0\} \\ \alpha_{Hjt} &= \{0, \quad 0.2, \quad 1\} \end{aligned}$

The β-s are coefficients and represent the doctor's responses to drug costs under the different funding plans.

When the market for TNF-apha inhibitors opened in 2000, Enbrel was fully covered by NIS (i.e. $\alpha_{I1t}=1$), whereas Remicade was covered by the hospitals ($\alpha_{H3t}=1$). In the fall 2002, the funding of Remicade changed. Hospitals had to pay 20 per cent, whereas NIS paid the remaining 80 per cent ($\alpha_{I3t}=0.8$, $\alpha_{H3t}=0.2$). When entering in 2003, Humira was given the same funding plan as Enbrel, i.e. fully coverage by NIS ($\alpha_{I2t}=1$). In June 2006, the government then gave the full funding responsibility to the hospitals for all three drugs (α_{Hjt}

=1 for all j.).

Because hospitals face budget constraints, the hospital's opportunity costs of drug treatment are strictly positive. Reduced treatment costs may benefit other activities and patients at the same hospital. With coverage by the national insurance plan, the direct opportunity cost of the hospital will be zero. Choosing a drug that is fully paid by the insurance plan has no impact on the resources available for other activities at the hospital. Doctors have guidelines that instruct them to be cost consciousness in their choices of treatment. Therefore, we expect doctors to be price responsive also in the case of insurance plan coverage. However, in the case where the hospital pays the treatment costs, we expect doctors to become more concerned about these costs. This might be due to the personal incentives of doctors' to economize on costs in order to be able to spend extra resources on other patients, or just due to the fact that the hospital management has stronger incentives to monitor the individual doctor's treatment choices when these involve hospitals own budgets.

Our hypothesis thus is that (remember that positive coefficients imply a negative impact of price on utility):

$$H_0: \quad b_H = b_I$$
$$H_I: \quad 0 < b_I < b_H$$

Because ε_{ijt} is assumed to be independently, identically extreme value distributed across individuals and products, the probability that the decision-making unit i will choose drug j at time t is given by the following multinomial logit probabilities:

$$(4) \qquad \varphi_{ijt} = \varphi_{jt} = \Pr\left(U_{ijt} = \underset{k=1,2,3}{\text{Max}}\, U_{ikt}\right) = \frac{\exp(-v_{jt} p_{jt} + a_{jt})}{\sum_{k=1}^{3} \exp(-v_{kt} p_{kt} + a_{kt})}; \quad j=1,2,3$$

We choose Enbrel to be the reference product, here denoted product 1, and if we assume there is no outside good whose utility can be normalized to zero, these probabilities can be written[4]:

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[4] Unfortunately, we are not able to construct an outside option to treatment with one of the three therapies. This would require a record of all patients with these diagnoses – including those without medical treatment. Our model, therefore, assumes that variations in prices covered by hospitals or the insurance schemes only affects the allocation of patients on different therapies (drugs), and not the total number of patients treated.

$$\varphi_{jt} = \frac{\exp(a_{jt} - a_{1t} - (v_{jt}p_{jt} - v_{1t}p_{1t}))}{1 + \sum_{k=2}^{3} \exp(a_{kt} - a_{1t} - (v_{kt}p_{kt} - v_{1t}p_{1t}))} \qquad j=2,3; \quad t=1.2....62$$

(5)

$$\varphi_{1t} = \frac{1}{1 + \sum_{k=2}^{3} \exp(a_{kt} - a_{1t} - (v_{kt}p_{kt} - v_{1t}p_{1t}))}$$

The observed parallel to the average of agents' probabilities, is the market share of the product, m_{jt}. Because we only exploit aggregate data, our observed variables will be the market shares.

The coefficient a_{jt} is assumed to depend on three parts: a deterministic drug-specific constant, α_j, a time trend, $\beta_j t$, and a stochastic variable e_{jt}. The deterministic drug-specific constants reflects some unobserved drug-specific elements, while the two others may reflect some factors related to doctors' perception of quality which may change over time and some of this is also unobserved.

This gives us the following log-odd ratios:

(6) $\qquad \log \dfrac{m_{2t}}{m_{1t}} = \alpha_2 - (v_{2t}p_{2t} - v_{1t}p_{1t}) + \beta_2 t + e_{2t}$

(7) $\qquad \log \dfrac{m_{3t}}{m_{1t}} = \alpha_3 - (v_{3t}p_{2t} - v_{1t}p_{1t}) + \beta_3 t + e_{3t}$

As mentioned in the introduction there are reasons to expect that qualtity aspects captured by the error terms, e_{2t} and e_{3t}, can correlate with prices. The empirical results, given in Section 5, confirms this expectation. We deal with this problem by modelling a simultaneous demand and pricesetting model.

We assume that each drug provider sets the price on its drug so that expected profit is maximized, given the market share equations for the three drugs and the prices set by the other two providers. In this approach we also account for a possible correlation between the error terms in the model. This means that in addition to control for quality being priced out in the market, we also control for a variety of unobserved heterogeneity.

The market share equations for all three drugs can be written as:

(8) $\quad m_{1t} = \dfrac{1}{1 + \displaystyle\sum_{j=2}^{3} \exp(\alpha_j - (v_{jt}p_{jt} - v_{1t}p_{1t}) + \beta_j t + e_{jt})}$

(9) $\quad m_{2t} = \dfrac{\exp(\alpha_2 - (v_{2t}p_{2t} - v_{1t}p_{1t}) + \beta_2 t + e_{2t})}{1 + \displaystyle\sum_{j=2}^{3} \exp(\alpha_j - (v_{jt}p_{jt} - v_{1t}p_{1t}) + \beta_j t + e_{jt})}$

(10) $\quad m_{3t} = \dfrac{\exp(\alpha_3 - (v_{3t}p_{3t} - v_{1t}p_{1t}) + \beta_3 t + e_{3t})}{1 + \displaystyle\sum_{j=2}^{3} \exp(\alpha_j - (v_{jt}p_{jt} - v_{1t}p_{1t}) + \beta_j t + e_{jt})}$

Note that we have:

(11) $\quad \dfrac{\partial m_{jt}}{\partial p_{jt}} = -v_{jt}m_{jt}(1 - m_{jt}); \quad j=1,2,3$

Expected profits of the seller of drugs are:

(12) $\quad \pi_{jt} = (p_{jt} - C_{jt})N_t m_{jt}$

Here C_{jt} are unobserved unit costs. In estimating the model we will assume that $C_{jt} = c_{jt} + \eta_{jt}$, where $c_{jt} = c_j$ will be estimated below and η_{jt} is an unobserved part of the unit cost and/or unobserved factors in the profit maximization process. N_t is the number of potential customers.

Maximizing expected profit with respect to price yield the following first order conditions:

(1 3) $p_{jt} = C_{jt} + \dfrac{1}{v_{jt}(1 - m_{jt})}; \quad j=1,2,3.$

The econometric model we estimate is given by the following set of equations:

$$(14) \quad \log \frac{m_{2t}}{m_{1t}} = \alpha_2 - (v_{2t}p_{2t} - v_{1t}p_{1t}) + \beta_2 t + e_{2t}$$

$$(15) \quad \log \frac{m_{3t}}{m_{1t}} = \alpha_3 - (v_{3t}p_{3t} - v_{1t}p_{1t}) + \beta_3 t + e_{3t}$$

$$(16) \quad p_{1t} = c_1 + \frac{1}{v_{1t}(1 - m_{1t})} + \eta_{1t}$$

$$(17) \quad p_{2t} = c_2 + \frac{1}{v_{2t}(1 - m_{2t})} + \eta_{2t}$$

$$(18) \quad p_{3t} = c_3 + \frac{1}{v_{3t}(1 - m_{3t})} + \eta_{3t}$$

where

$$v_{jt} = \alpha_{Ijt}\beta_I + \alpha_{Hjt}\beta_H; \quad i = 1,2,3$$

We will allow for correlation across the random variables. The correlation structure is the following:

$$(19) \quad e_{2t} = \rho_2 \eta_{2t} + \mu_{2t}$$

$$(20) \quad e_{3t} = \rho_3 \eta_{3t} + \mu_{3t}$$

$$(21) \quad \eta_{1t} = \rho_{12}\eta_{2t} + \rho_{13}\eta_{3t} + \mu_{1t}$$

where
μ_{it} is normally distributed $N(0, \sigma_i)$.

From (17) and (19) we get:

$$(22) \quad e_{2t} = \rho_2 \left(p_{2t} - c_2 - \frac{1}{v_{2t}(1 - m_{2t})} \right) + \mu_{2t}$$

From (18) and (20) we get

$$(23) \quad \varepsilon_{3t} = \rho_3 \left(p_{3t} - c_3 - \frac{1}{v_{3t}(1 - m_{3t})} \right) + \mu_{3t}$$

And finally we have

$$(24) \quad \eta_{1t} = \rho_{12} \left(p_{2t} - c_2 - \frac{1}{v_{2t}(1 - m_{2t})} \right) + \rho_{13} \left(p_{3t} - c_3 - \frac{1}{v_{3t}(1 - m_{3t})} \right) + \mu_{1t}$$

The endogenous (stochastic) variables in our model is the market shares and the prices. In order to derive the distribution of these variables, given the distribution of the

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error terms in the equations above, we have to obtain the probability law of the observed random variables, $\{m_{1t}, m_{2t}, m_{3t}, p_{1t}, p_{2t}, p_{3t}\}$. Basically this means that we multiply into the likelihood of the sample the numerical value of the Jacobian of transformation[5]. The Jacobian determinant gives the derivatives of of the error terms in each of the 6 equations above with respect to the 6 observed random variables present in the equations. If the Jacobian determinant explicitly depends on the unknowm coefficients that we estimate, then it matters for the estimation to include the absolute value of the Jacobian determinant. This is the case here.The likelihood that we maximize with respect to the unknown coefficients is given in (25). In estimating the model the three c-s are assumed to be constant over time.

$$
(25) \quad L = \prod_{t=1}^{62} \frac{1}{\sigma_2} f\left(\frac{\log(m_{2t}) - \log(m_{1t}) - \alpha_2 + (v_{2t}p_{2t} - v_{1t}p_{1t}) - \beta_2 t - \rho_2\left(p_{2t} - c_{2t} - \frac{1}{v_{2t}(1 - m_{2t})}\right)}{\sigma_2} \right)
$$

$$
\times \frac{1}{\sigma_3} f\left(\frac{\log(m_{3t}) - \log(m_{1t}) - \alpha_3 + (v_{3t}p_{3t} - v_{1t}p_{1t}) - \beta_3 t - \rho_3\left(p_{3t} - c_{3t} - \frac{1}{v_{3t}(1 - m_{3t})}\right)}{\sigma_3} \right)
$$

$$
\times \frac{1}{\sigma_1} f\left(\frac{p_{1t} - c_{1t} - \frac{1}{v_{1t}(1 - m_{1t})} - \rho_{12}\left(p_{2t} - c_{2t} - \frac{1}{v_{2t}(1 - m_{2t})}\right) - \rho_{13}\left(p_{3t} - c_{3t} - \frac{1}{v_{3t}(1 - m_{3t})}\right)}{\sigma_1} \right)
$$

$$
\times \frac{1}{\sigma_{\eta 2}} f\left(\frac{p_{2t} - c_{2t} - \frac{1}{v_{2t}(1 - m_{2t})}}{\sigma_{\eta 2}} \right)
$$

$$
\times \frac{1}{\sigma_{\eta 3}} f\left(\frac{p_{3t} - c_{3t} - \frac{1}{v_{3t}(1 - m_{3t})}}{\sigma_{\eta 3}} \right)
$$

$$
\times \left| J_t \right|
$$

where f(.) is the unit normal probability density and $\left| J_t \right|$ is the absolute value of the determinant of the Jacobian given by

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[5] See Haavelmo (1944), p 87.

$$(26) \quad |J_t| = \begin{vmatrix} \dfrac{m_{1t}+m_{2t}}{m_{1t}m_{2t}} & \dfrac{1}{m_{1t}} & -v_{1t} & v_{2t} & 0 \\[2mm] \dfrac{1}{m_{1t}} & \dfrac{m_{1t}+m_{3t}}{m_{1t}m_{3t}} & -v_{1t} & 0 & v_{3t} \\[2mm] -\dfrac{1}{v_{1t}(1-m_{1t})^2} & -\dfrac{1}{v_{1t}(1-m_{1t})^2} & 1 & 0 & 0 \\[2mm] -\dfrac{1}{v_{2t}(1-m_{2t})^2} & 0 & 0 & 1 & 0 \\[2mm] 0 & -\dfrac{1}{v_{3t}(1-m_{3t})^2} & 0 & 0 & 1 \end{vmatrix}$$

The model extended to allow for autocorrelation and the results for this extended model are given in Appendix A.

4. Data

There are three biotechnological drugs acting as *t*umor *n*ecroses *f*actor (TNF) alpha inhibitor in the treatment of rheumatoid arthritis (RA). Enbrel (etanercept), is a recombinant protein of human origin. It was approved by the Food and Drug Administration (FDA) in 1998 for the reduction of signs and symptoms of moderate to severe RA, and in Europe by European Medicin Agency (EMEA) in 1999. It is administered twice a week by subcutaneous injection. At the time of introduction, it was indicated for use by patients who had an inadequate response to one of the other disease-modifying anti-rheumatic drugs (DMARD) (Moreland et al., 1997). In combination with Rheumatrex (methotrexate) clinical trials proved that the addition of etanercept to methotrexate therapy resulted in rapid and sustained improvement (Weinblatt et al., 1999). Enbrel gained approval also for the treatment of juvenile RA and psoriatic arthritis, and further studies demonstrated its effectiveness as compared with methotrexate in patients with early active RA (Bathon et al., 2000), making it a first-line treatment for RA and a leading brand within the new class of DMARDs. Enbrel was developed by Immunex, a biotechnology company that in 2001 was acquired by Amgen.

The second TNF-based RA product on the market is Remicade (infliximab), a chimeric (human and mouse) monoclonal antibody that proved to be safe and effective with persistently active RA not responding to methotrexate therapy (Lipsky et al., 2000). It is marketed by Centocor together with Schering Plough and the Japanese company Mitsubishi Tanabe Pharma. In Europe EMEA granted marketing authorization in March 2000. It is administered every four to eight weeks via an intravenous infusion that may take several hours to complete and requires qualified personnel monitoring of adverse reactions. This is considered as a disadvantage in comparison with Enbrel. Nevertheless, Remicade progressively increased its sales gaining high market shares. Price of Remicade is lower than Enbrel.

The third TNF alpha inhibitor in the market is Humira (adalimumab), a fully human monoclonal antibody approved by FDA in December 2002 and by EMEA in September 2003, and marketed by Abbott in the form of subcutaneous injection every two weeks, setting the drug price in parity with Enbrel. Its attracting dosing profile was considered a key success factor, but relatively short after its launch, the growth of sales slowed and it seemed not to threaten significantly the market position of its two competitors.

Market penetration in terms of sales value of these three drugs has been highly successful in Norway. Sale of Enbrel, Remicade and Humira accounted for 8 per cent of total pharmaceutical sale in Norway in 2008.[6]

The dataset consists of monthly wholesale value and quantity sold, expressed in defined daily doses (DDD), for each of the three drugs Enbrel, Remicade and Humira.[7] The data set covers the months from January 2000 to March 2008, indicated as running from t=1 to t=99 in Figures 1 and 2 below. The price per DDD is constructed from combining the value and quantity information. Figure 1 shows the monthly wholesale value of sale.

The market opened early 2000, with the entry of both Enbrel and Remicade. Enbrel had a far stronger growth during the first year, and became soon the leading drug. In 2001-2002 Enbrel experienced problems of supplying the global market. Worldwide

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[6] Norwegian Association of Pharmaceutical Manufacturers. Facts and Figures (2009).
[7] The data set is provided by Farmastat, a company owned by Norwegian Association of Pharmaceutical Manufacturers.

capacity shortage forced the producer to reduce the sale of Enbrel in Norway. This explains the drastic reduction in sale value for Enbrel, and its volatility shown in Figure 1.
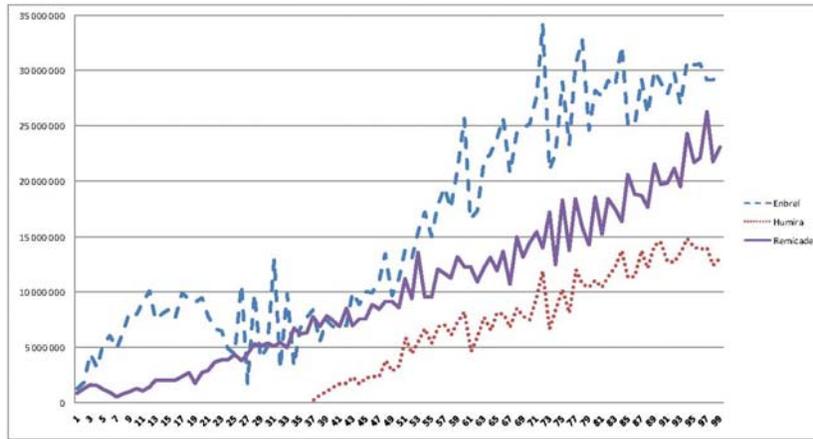

Figure 1: Monthly wholesale value of sale; 1000 NOK. As of April 2012 1 Euro~NOK 7.6

In the fall 2003, the third drug, Humira, entered. Although Humira experienced a steady growth in the fast growing market, it never succeeded in capturing a larger market share. Figure 2 shows the development of market shares.
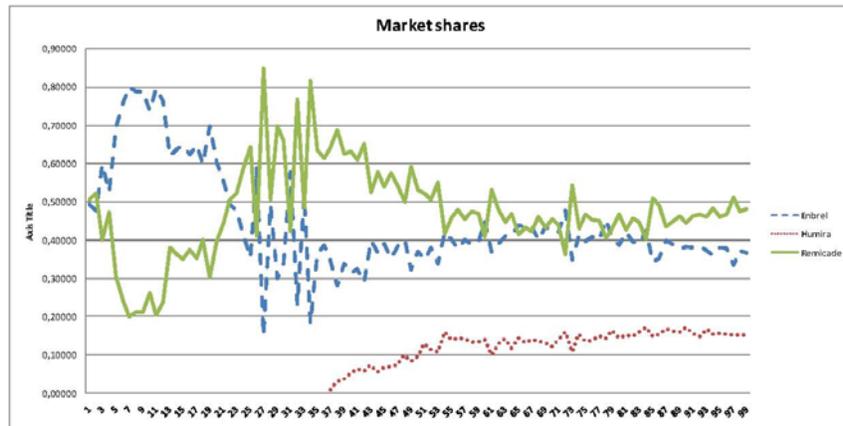

Figure 2: Market shares for the three drugs (DDD).

Within the first year, Enbrel reached a market share of 80 percent. The market share dropped rapidly, most triggered by the abovementioned shortage of production capacity. Since Remicade was the only alternative TNF-inhibitor in this period, it

experiences an equivalent rise in its market share. Humira reached a market share close to 9 percent after a few months.

The price of Enbrel has always been very high relative to Remicade. Except for the first couple of months, the wholesale price of Enbrel per DDD stayed between 350 and 400 NOK until late fall 2001. Then the price dropped to a level closer to 300 NOK per DDD. Remicade started out with a price of 200 per NOK, but came down to a level between 160 and 170 NOK per DDD after a few months. Humira entered with a price much above the price of Enbrel. Although Humira has kept its position as the price leader, the price gap (compared with Enbrel) has been narrowed during the sample period. Figure 3 shows the development of wholesale prices. As mentioned in the introduction. Enbrel, Humira and Remicade had different and varying funding schemes over time.
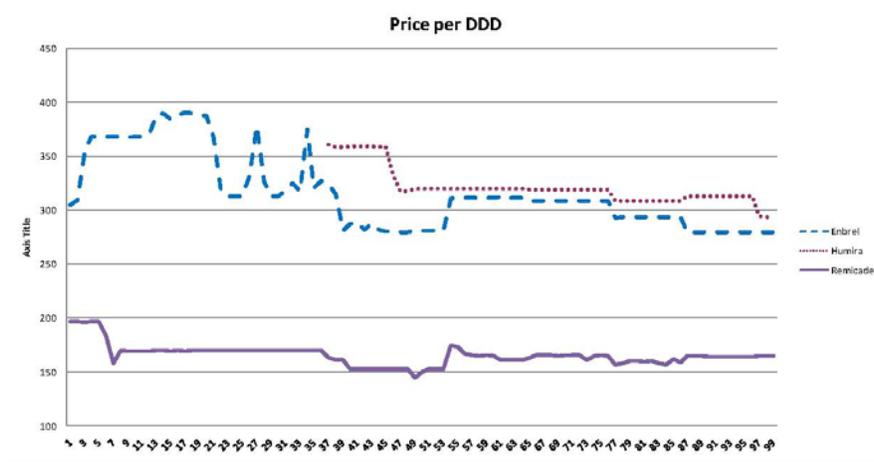
Figure 3. Wholesale price, NOK per DDD.

We have chosen to restrict the sample period in our empirical analysis to t=38-99 for several reasons. First, there are reasons to expect demand behavior – and in particular price responses – to be different in the early stage of a new pharmaceutical market compared with the more maturated market. In the early stage, doctors are unfamiliar with the particular technology of treatment (TNF-alpha inhibitors) – both its efficiency and its possible side-effects. In a more mature market, doctors have gained experience with the

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drug, and will be better able to make treatment choices for the individual patients.[8] Gaining experience with TNF-inhibitors, the doctors will be better able to take treatment costs into account when choosing between the available alternatives. Second, capacity shortage for the manufacture of Enbrel during the first years distorts demand. As seen in this Section, Enbrel experienced a sharp decline in sale 2001-2002 that was due to a global capacity problem of the manufacture. After a period of decline, sale and market shares were very unstable, until problems were resolved some months before the entry of Humira.

Summary statistics for the sample used in estimating our models are provided in Table 1.

Table 1. Summary statistics (62 obs)

Variable	Mean	Std. Dev.	Min	Max
Enbrel:				
DDD	73413.7300	28228.5300	17534.0000	111829.0000
market share	0.3860	0.0379	0.2802	0.4764
price	0.2942	0.0136	0.2794	0.3146
sales	21572.0700	8128.4650	5515.4780	34216.2800
α_{H1}	0.3548	0.4824	0.0000	1.0000
α_{I1}	0.6452	0.4824	0.0000	1.0000
Humira:				
DDD	26143.3400	13833.7300	2014.0000	47531.0000
market share	0.1278	0.0362	0.0322	0.1720
price	0.3206	0.0163	0.2935	0.3591
sales	8206.7740	4197.8050	722.3141	14838.1300
α_{H2}	0.3548	0.4824	0.0000	1.0000
α_{I2}	0.6452	0.4824	0.0000	1.0000
Remicade:				
DDD	88812.0800	30046.7300	43019.0000	159655.0000
market share	0.4862	0.0651	0.3639	0.6876
price	0.1608	0.0056	0.1446	0.1743
sales	14341.7000	5026.1530	6901.8260	26308.0300
α_{H3}	0.4839	0.3859	0.2000	1.0000
α_{I3}	0.5161	0.3859	0.0000	0.8000

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[8] See Berndt et al. (2003).

5. Results

First, we show the estimates of the coefficients $\{\alpha_2, \alpha_3, \beta_I, \beta_H, \beta_2, \beta_3\}$ when only the demand model is used (Table 2).

Table 2. The demand model

Coefficients	Estimates	t-values
β_I	2.652	2.90
β_H	4.513	3.93
β_2 (Humira)	0.014	11.30
β_3 (Remicade	-0.011	-4.77
α_2 (Humira)	-2.066	-20.49
α_3 (Remicade)	0.587	3.03
Number of observations	62	
R^2 (Humira)	0.7476	
R^2 (Remicade)	0.2351	

The point estimates imply that $\beta_I < \beta_H$, but the 95 per cent confidence intervals overlap: Lower limit for β_I is 0.8581 and upper limit is 4.4450, and for β_H the lower limit is 2.2627 and the upper limit is 6.7633. The problem with this estimation is that the error terms in the market share equations may be correlated with the prices. There are several reasons for this and one is that prices are set by the drug providers so that unobserved quality aspects are priced out. When regressing the predicted squared residuals against prices we get significant results which clearly indicate that homoscedasticity is rejected. Berry et al (1995) recommend that the constants in the equations above should vary across observations and hence represent the unobserved quality attributes that may be correlated with price. Next, these coefficients should be regressed against prices, or calibrated. The problem in our case with that approach is the high number of constants; here equal to the number of observations. We have therefore chosen to model demand and the price setting of drugs and estimate market shares and price setting equations simultaneously. The estimates are given in Table 3.

Table 3. Joint estimates of market shares and price setting

Coefficents	Estimates	t-values
β_I	11.645	37.02
β_H	13.022	30.57
β_2 (Humira)	1.161	6.46
β_3 (Remicade)	-0.032	-0.08
α_2 (Humira)	-1.635	-13.05
α_3 (Remicade)	-1.340	-4.705
c_1	0.159	36.76
c_2	0.226	66.36
c_3	~0	~0
σ_1	0.010	11.01
σ_2	0.187	11.01
σ_3	0.176	4.02
$\sigma_{\eta2}$	0.017	10.93
$\sigma_{\eta3}$	0.032	10.56
ρ_2	3.718	1.93
ρ_3	-4.901	-1.69
ρ_{12}	-0.177	-1.36
ρ_{13}	-0.078	-1.025
Log Likelihood	1055.700	
No of observations	62	

Now, the predicted values of the squared residuals in the market share equations do not vary significantly with prices and thus homoscedasticity is **not** rejected. The 95 per cent confidence intervals for the β_I and β_H do overlap just a little:lower limit for β_I is 11.018 and the upper limit is 12.2785, and for β_H the lower limit is 12.1640 and the upper limit is 13.8808. A 90 per cent interval does not overlap: lower limit for β_I is 11.1276 and the upper limit is 12.1624, and for β_H the lower limit is 12.3214 and the upper limit is 13.7266. Based on this model there are some clear evidences that doctors are more responsive when the hospitals cover the expenses compared to when national insurance is taking up the bill.

In Appendix A we report the results when the model is extended to deal with autocorrelation in all error terms. The estimates of the autoregressive coefficients are all positive, between 0 and 1, and clearly significant. More importantly, the estimates of β_I and β_H do not change much.

When autocorrelation is accounted for the trend effects in market shares (β_2 and β_3) both are insignificant. The drug specific constants (α_2 and α_3) are estimated to be negative (relative to Enbrel). Now both are significant and the numerical values becomes higher, in particular for Remicade. These results indicate that given the price, Enbrel is a favored drug in particular compared to Remicade. This accord with the fact that Enbrel yields a more efficient treatment and require less time use for the patient, and with less side effects, than Remicade.

All unit costs are now significant and almost of the same magnitude as in Table 3, in particular for Enbrel and Humira. To account for autocorrelation, have no clear impact on the estimates of the variances of the error terms. However, the correlation between the unobserved factors in the market share of Remicade and its price setting is now estimated to be significantly negative. Also the correlation between the unobserved factors in the pricesetting of Enbrel and Remicade is estimated to be significantly negative. The first means that if there is negative shock in the price of Remicade, then its market share increases, cet.par. The latter estimate implies that a negative price shock for Remicade has a positive impact on the prices of Enbrel. However, it should be noticed that due to the observed part in the pricesetting equation for Enbrel a lower price of Remicade implies also a negative price response for Enbrel. This is due to the monopolistic competition among the three producers. The negative correlation between the unobserved factors in the pricesetting of Enbrel and Remicade modifies this price response and is obviously due to unobserved quality characteristc across the two drugs. The better quality of Enbrel makes it possible to reduce the price less as a response to a negative shift in the price of Remicade. This lesser response is here captured by the probabilistic structure of the pricesetting part in the model.

To further compare the results of the three models we show mean own-price elasticities. These elasticities are the elasticities of expected demand with respect to the prices p_{jt}. The elasicities are calculated by applying the following expression:

$$(27) \quad E_{jt} = \frac{p_{jt}}{m_{jt}} \frac{\partial \hat{m}_{jt}}{\partial p_{jt}} = -v_{jt} p_{jt} (1 - \hat{m}_{jt}); \quad j=1,2,3$$

Here the market shares are the predicted shares using the whole structural parts in the different models. In Table 4 we give the means over the periods in the sample.

Table 4. Mean price elasticities

	The market share model	Demand and price setting approach	As the previous one, with autocorr.
Enbrel	-0.59`	-2.19	-2.34
Humira	-0.92	-3.39	-3.63
Remicade	-0.29	-1.02	-1.09

We cleary see that when unoberved quality and hence, statistical endogeneity, is controlled for, the numerical value of the price elasticities increases, To account for autocorrelation has a negligible impact on the elasticities.

6. Conclusions

We have employed a discrete choice model in which the doctor's choice among TNF-alpha inhibitors depends on the prices. Price response is allowed to vary with the identity of the third-party payer, national insurance and hospitals. The estimate of the resulting market share model indicates that homoscedasticity is rejected, which may be due to neglected unobserved quality aspects of the drugs which are priced out in the market. The traditional way of dealing with this problem is to instrument the prices. We have used another approach. We have modeled the market equilibrium for the three drugs. Prices are determined in a non-cooperative Nash – equilibrium. We include correlation between market share equations and price setting equations. We also account for autocorrelation by estimating an AR1 model. The equilibrium model is estimated in a joint maximum likelihood approach. The results show that homoscedasticity is not rejected. We find that doctors are significantly more responsive when the costs are covered by the hospitals compared to when costs are covered by national insurance. Moreover, the numerical values of the own-price elasticities increase substantially when a market share model is replaced by a market equilibrium model.

Appendix A. The market model extended to deal with autocorrelation.

To simplify notation let $Y_{2t} = \dfrac{\log m_{2t}}{\log m_{1t}}$, $Y_{3t} = \dfrac{\log m_{3t}}{\log m_{1t}}$, and let r_j, $j=2,3,4,5,6$ be the coefficients that capture the possible correlation over time between the error terms in the eqs (14)-(18) above. For instance $e_{2t}=r_2\, e_{2t-1}+ e^*_{2t}$, where * indicate the new error terms after assuming a first order autoregressive scheme. The equvivalent to eqs. (14)-(18) is then

$$(14^*)\quad Y_{2t}=r_2 Y_{2t-1} - (v_{2t}p_{2t} - v_{1t}p_{1t})+r_2(v_{2t-1}p_{2t-1} - v_{1t-1}p_{1t-1})+\beta_2(1-r_2)t + r_2\beta_2 +(1-r_2)\alpha_2 +e^*_{2t}$$

$$(15^*)\quad Y_{3t} = r_3 Y_{3t-1} - (v_{3t}p_{3t} - v_{1t}p_{1t})+r_3(v_{3t-1}p_{3t-1} - v_{1t-1}p_{1t-1})+\beta_3(1-r_3)t + r_3\beta_3 +(1-r_3)\alpha_3 +e^*_{3t}$$

$$(16^*)\quad p_{1t} = r_4 p_{1t-1} + (1-r_4)c_1 + \frac{1}{v_{1t}(1-m_{1t})} - r_4 \frac{1}{v_{1t-1}(1-m_{1t-1})} + \eta^*_{1t}$$

$$(17^*)\quad p_{2t} = r_5 p_{2t-1} + (1-r_5)c_2 + \frac{1}{v_{2t}(1-m_{2t})} - r_5 \frac{1}{v_{2t-1}(1-m_{2t-1})} + \eta^*_{2t}$$

$$(18^*)\quad p_{3t} = r_6 p_{3t-1} + (1-r_6)c_3 + \frac{1}{v_{3t}(1-m_{3t})} - r_5 \frac{1}{v_{3t-1}(1-m_{3t-1})} + \eta^*_{3t}$$

where as before

$$v_{jt} = \alpha_{Ijt}\beta_I + \alpha_{Hjt}\beta_H; \quad i=1,2,3$$

The likelihood now becomes

$$L = \prod_{t=1}^{62} \frac{1}{\sigma_2} f\left(\frac{\begin{array}{c} Y_{2t} - r_2 Y_{2t-1} + (v_{2t}p_{2t} - v_{1t}p_{1t}) - r_2(v_{2t-1}p_{2t-1} - v_{1t-1}p_{1t-1}) - \beta_2(1-r_2)t - r_2\beta_2 - (1-r_2)\alpha_2 - \\[4pt] - \rho_2\left(p_{2t} - r_5 p_{2t-1} - (1-r_5)c_2 - \dfrac{1}{v_{2t}(1-m_{2t})} + r_5 \dfrac{1}{v_{2t-1}(1-m_{2t-1})} \right) \end{array}}{\sigma_2} \right)$$

$$\times \frac{1}{\sigma_3} f\left(\frac{\begin{array}{c} Y_{3t} - r_3 Y_{3t-1} + (v_{3t}p_{3t} - v_{1t}p_{1t}) - r_3(v_{3t-1}p_{3t-1} - v_{1t-1}p_{1t-1}) - \beta_3(1-r_3)t - r_3\beta_3 - (1-r_3)\alpha_3 - \\[4pt] - \rho_3\left(p_{3t} - r_6 p_{3t-1} - (1-r_6)c_3 - \dfrac{1}{v_{3t}(1-m_{3t})} + r_5 \dfrac{1}{v_{3t-1}(1-m_{3t-1})} \right) \end{array}}{\sigma_3} \right)$$

$$\times \frac{1}{\sigma_1} f\left(\frac{\begin{array}{c} p_{1t} - r_4 p_{1t-1} - (1-r_4)c_1 - \dfrac{1}{v_{1t}(1-m_{1t})} + r_4 \dfrac{1}{v_{1t-1}(1-m_{1t-1})} - \rho_{12}\left(p_{2t} - r_5 p_{2t-1} - (1-r_5)c_2 - \dfrac{1}{v_{2t}(1-m_{2t})} + r_5 \dfrac{1}{v_{2t-1}(1-m_{2t-1})} \right) - \\[4pt] - \rho_{13}\left(p_{3t} - r_6 p_{3t-1} - (1-r_6)c_3 - \dfrac{1}{v_{3t}(1-m_{3t})} + r_5 \dfrac{1}{v_{3t-1}(1-m_{3t-1})} \right) \end{array}}{\sigma_1} \right)$$

$$\times \frac{1}{\sigma_{\eta 2}} f\left(\frac{p_{2t} - r_5 p_{2t-1} - (1-r_5)c_2 - \dfrac{1}{v_{2t}(1-m_{2t})} + r_5 \dfrac{1}{v_{2t-1}(1-m_{2t-1})}}{\sigma_{\eta 2}} \right)$$

$$\times \frac{1}{\sigma_{\eta 3}} f\left(\frac{p_{3t} - r_6 p_{3t-1} - (1-r_6)c_3 - \dfrac{1}{v_{3t}(1-m_{3t})} + r_5 \dfrac{1}{v_{3t-1}(1-m_{3t-1})}}{\sigma_{\eta 3}} \right)$$

$$\times |J_t|$$

where f(.) is the unit normal probability density and $|J_t|$ is the absolute value of the same determinant of the Jacobian as before. The estimates are given in Table A.1 below.

Table A.1. Joint estimates of market shares and price setting, accounting for autocorrelation.

Coefficents	Estimates	t-values
β_I	12.842	7.75
β_H	13.368	7.86
β_2 (Humira)	0.556	1.68
β_3 (Remicade)	0.836	0.95
α_2 (Humira)	-2.400	-2.51
α_3 (Remicade)	-8.868	-0.91
c_1	0.167	10.27
c_2	0.223	17.47
c_3	0.111	2.69
σ_1	0.007	10.74
σ_2	0.129	9.51
σ_3	0.104	8.03
$\sigma_{\eta2}$	0.005	10.51
$\sigma_{\eta3}$	0.018	6.83
ρ_2	3.649	0.88
ρ_3	-10.040	-7.94
ρ_{12}	-0.048	-0.25
ρ_{13}	-0.299	-5.26
r_2	0.691	7.60
r_3	0.890	17.18
r_4	0.664	6.36
r_5	0.878	24.34
r_6	0.662	2.87
Log Likelihood	1225.700	
No of observations	61	

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