Cost containment by peer prior authorization program for second line treatment in patients with retinal disease

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Abstract

Background: Rising drug prices prompt the establishment of cost-containment treatment policies. Ranibizumab was approved for treatment of retinal diseases, although the less-costly, off label, bevacizumab has been found equally effective. We describe a novel prior-authorization approach, which we applied to ranibizumab as second-line treatment, in non-responders to first-line bevacizumab: A steering committee set the funding criteria based on cost and updating clinical considerations; an ophthalmic specialists team evaluated their colleagues’ individual patient subsidization request, based on the funding criteria.

Methods This retrospective cohort included all the applications for a first or ongoing treatment with ranibizumab, for one or both eyes, applying for treatment between March 1, 2012 to December 31, 2015 During that time, 16,778 applications for funding from 5,642 patients (~2.97 applications/patient) were submitted and assessed, accounting for 31% of bevacizumab (first line)-treated patients A approval was granted in 94.6% of all requests, via their peer-revision.

Conclusions The program made it feasible to finance a costly treatment for patients that may benefit from it, while maintaining qualitative medical outcomes and sparing treating ophthalmologist from ethical gatekeeping dilemmas.

Background

Rising drug costs and the aging population in high-income countries pose cost-containment challenges to healthcare systems.(1) Increasing patient co-payments for more expensive drugs can lead to the decreased or discontinued use of essential medications.(2) An alternative solution is the formulation of prior-authorization policies for specific drugs, which have been shown to increase economic savings in health maintenance organizations (HMOs) by reducing expensive and unnecessary drug
Visual impairment and blindness pose a serious medical, social and economic burden. Prompted by studies showing that anti-vascular endothelial growth factor (anti-VEGF) slows the progression of vision loss in patients with various retinal diseases, Genentech Inc. (South San Francisco, USA) developed two anti-VEGF drugs: bevacizumab (Avastin®), marketed by Roche (Basel, Switzerland) and ranibizumab (Lucentis®), marketed by Novartis (Basel, Switzerland). Only the costlier ranibizumab has been approved by the U.S. Food and Drug Administration and the European Commission for intraocular use. However, given that both drugs were found equally effective and safe for the treatment of age-related macular degeneration (AMD) and equally effective for the treatment of diabetic retinopathy, a policy directed at increasing the first-line use of bevacizumab is not expected to pose a clinical disadvantage. Moreover, switching from one anti-VEGF drug to another has been shown to benefit certain patients. For example, ranibizumab was proven as effective in patients with diabetic macular edema (DME) or AMD who failed to respond to bevacizumab. Therefore, the off-label first-line use of bevacizumab is growing worldwide. Indeed, according to a study from the U.S., off-label drug use in general accounts for 21% of all commonly prescribed medications.

In Israel, the National Health Insurance Law provides universal, high-quality, government-subsidized coverage of an approved medical services, drugs and equipment, denoted health "basket", for all citizens and residents in the country. The contents of the basket are reviewed yearly by a dedicated committee of healthcare professionals and public figures. Addition of novel treatments and technologies is determined based on expected patient benefits, patient load and projected costs. Individual medical services are allocated by four national nonprofit HMOs. Membership in any HMO is mandatory. Members pay a minimum health tax and select their HMO for the basic basket services,
and they may also purchase supplementary health plans through the HMO and/or the private sector.

Clalit Health Services is the largest HMO in Israel, insuring more than 53% of the population (approximately 4.3 million members as of 2014). About 70% of Clalit Health Services members owned its supplementary health plan, "Clalit Mushlam", in the beginning of this study. Treatments not included in the basket, that are covered by Clalit Mushlam, are determined by a steering committee of medical professionals, health administrators and health economists. Final decisions are based on estimated clinical and financial data. Applications for these out-of-the-basket treatments for individual patients are submitted by treating physicians. These are being sent for revision by selected physicians, which decide upon approval of subsidization, according to the criteria determined by the steering committee of Clalit Mushlam.

In 2008, Clalit Health Services added bevacizumab for the off-label treatment of retinal diseases to its list of medications offered almost free-of-charge to members. The indications for bevacizumab were AMD, DME, and central and branch retinal vein occlusions (CRVO and BRVO, respectively). In March 2012, ranibizumab was authorized for use on the HMO’s supplementary plan, Clalit Mushlam, for the identical indications of bevacizumab, in case of retinal diseases. Expected costs were assessed in advance, taking into account the co-payments of 100$ by the patient. Notably, one injection of ranibizumab in the Israeli private sector costs ~$1,600, which is more than the monthly pension of most retirees, the largest potential population expected to need ranibizumab. Insufficient response to bevacizumab treatment, in one or both eyes, led the treating ophthalmologist to request for ranibizumab subsidization by the HMO. This raised the need for a sensitive review by fellow specialists, according to the clinical decision-making protocol, determined by the Clalit Mushlam steering committee.
In this study, we describe a novel approach for peer-examination process of ranibizumab treatment recommendation in retinal diseases. The clinical criteria for ranibizumab prescription, determined by the steering committee, were updated in an ongoing manner based on scientific publications. In this manner, treating ophthalmologists avoid the ethical dilemmas inherent in serving as gatekeepers. This process maintained professional guidelines and offered patients optimal treatment, while preserving a budgeting framework.

Methods

The study was approved by the Clalit institutional community review board. The study cohort included all the applications for a first or ongoing treatment with ranibizumab, for one or both eyes, of Clalit Mushlam members from March 1, 2012 to December 31, 2015.

Steering committee for ranibizumab subsidization

To examine the possibility of coverage of ranibizumab by Clalit Mushlam in 2012, a steering committee was assigned and assembled to determine indications, to set funding protocol for ranibizumab treatment and to estimate the expenses expected from the program.

This committee was comprised of four medical professionals (three leading ophthalmologists and a leading neurologist), three health administrators (two medical doctors and a pharmacist) and three health economists.

Indications of prior authorization
The steering committee established treatment and funding protocols for retinal diseases, including AMD, DME and CRVO/BRVO.

The clinical indications for the drug were updated, corresponding to the terms of the supplementary program regulations, when new treatment protocols were issued by the U.S. Federal Drug Administration (efficiency level I or IIa, and strength of evidence A or B, according to Micromedex database) or by the Israel Ministry of Health. Therefore, later in February 2014, choroidal neovascularization in pathologic myopia was added to the indications list, according to evidence-based knowledge accumulated in the literature and Micromedex database.

Criteria for prior authorization

Bevacizumab was designated the first-line treatment.

Candidates for switching to ranibizumab treatment were defined as members of Clalit Mushlam, who failed to respond to bevacizumab after $\geq 3$ consecutive injections (in the same eye), with 4-6 weeks intervals between injections during the last 6 months, that were administered in a public hospital. Bevacizumab failure was defined as at least one of the followings: (i) optical coherence tomography (OCT) findings of increased central retinal thickness in addition to presence of fluids, (ii) disease-related decrease in visual acuity by more than one line, (iii) decreased central retinal thickness of $<50$ microns or $<10\%$ in the presence of edema, (or (iv) toxic or inflammatory reaction to bevacizumab.

In patients that were previously granted with ranibizumab treatment, the treating ophthalmologist could request its continuation in cases that ranibizumab was the last drug administered and a good response was found after 3 consecutive injections. A good response was determined as (i) improvement in central retinal thickness according to OCT, of $>50$ microns or $>10\%$ or (ii) improvement in visual acuity due to improvement in retinal
fluids, after first 3 ranibizumab consecutive injections, or (iii) stabilization of these parameters after >2 ranibizumab treatment series.

Applications for ranibizumab treatment funding were rejected, due to lack of improvement during ranibizumab treatment, missing patient data (injection dates, visual testing and OCT findings before and after the treatment with ranibizumab), toxic or inflammatory reaction to ranibizumab, ocular or systemic adverse events, or diagnosis other than those approved.

Patients who did not meet these criteria, according to submitted data, or failed to respond to ranibizumab treatment in the past, were rejected for ranibizumab funding.

Data collection

For purposes of this study, the details of the applications for ranibizumab treatment submitted to Clalit Health Services and all the information provided on the application forms, including medical parameters that were relevant to the approval process, were collected. Applications that were missing data relevant for documentation were excluded. The data were uploaded to an electronic file in encrypted form to conceal the patients' identity. Descriptive summaries and statistical analyses were generated using Python 2.7.12 language via Scikit-learn library.

Results

Process of requests submission for ranibizumab funding

We phrased an approval application form for the request of ranibizumab treatment funding (Figure 1). This application was submitted to the ophthalmic specialists team by the treating ophthalmologists employed at any of the 20 public hospital-affiliated retina units in the country, that treat individuals insured by Clalit Mushlam. Although usually not needed, supplementary medical records about the patients were sent directly from the
retina units or the primary clinic in the community.

When all the required data were submitted, the form was forwarded to be evaluated by the ophthalmic specialists team by its representatives. This team used the information supplied on the application forms to assess the effectiveness of the treatment so far, as well as the need to start, continue, or renew ranibizumab administration. Notably, neither the ophthalmic specialists team nor the treating ophthalmologists requesting the funding, were provided with information regarding the program’s financial considerations of the steering committee and the expenses of by Clalit Mushlam. The patient, primary care unit personnel, and retina unit personnel are all blinded to the identity of the ophthalmic specialists that examined the application. The responses to the applications were sent via email, along with explanations, if necessary, to the patient's primary care physician and to the retina unit treating ophthalmologist who submitted the application form (Figure 2). A single funding approval covered 3 injection administrations and expired after 6-months period. The co-payment for patients prescribed ranibizumab, determined according to the regulations of Clalit Mushlam, was about $100 per injection (The drug and its administration's costs).

In patients that funding for the treatment with ranibizumab was denied, the treating ophthalmologists could either continue with bevacizumab injections, stop treatment or send an amended application form for re-evaluation of the request, if additional data were available (Figure 2).

Yield of the ranibizumab approval process

According to an external report supplied by Clalit Health Services prior to the study period, about 22,000 individuals were treated for retinal diseases with bevacizumab in 2011. By their estimation, they received about 200,000 injections annually in total.
Approximately 18,000 bevacizumab-treated patients (82%) had supplementary Clalit Mushlam insurance, accounting for 164,000 bevacizumab injections. The steering committee estimated the consumption of ~16,000 vials of ranibizumab annually, based on: (i) the numbers of Clalit Mushlam patients treated with bevacizumab, (ii) expected compliance of treating ophthalmologists and ophthalmic experts to the guidelines, (iii) adherence of patients to the treating ophthalmologists' recommendations, (iv) accepted treatment protocols for ranibizumab by each diagnosis, and (v) expected learning curve of the funding process by the treating ophthalmologists.

After the establishment of requests submission process for ranibizumab funding, Clalit Mushlam announced it to the managers of all retina units in all public hospitals in Israel. Our study included all 5,642 patients (31% of bevacizumab-treated members of Clalit Mushlam), that applied for second-line ranibizumab treatment by a treating ophthalmologist in a public hospital-affiliated retina unit in Israel. These patients included 2,867 females (51%) and 2,755 males (49%) patients of mean age 75.3 (SD = 11.13) years (Table 1). A total of 16,778 applications for the initiation or continuation of ranibizumab treatment in these patients were submitted for evaluation to the ophthalmic specialists team. The rate of application submission was 2.97 applications per patient. The requests submission rate was few requests at the beginning of the study, elevated up to 528 requests per month and its average was 357 requests per month throughout the study period (Figure 3). The entire process, from submission of the application form to either approval or rejection of the request, was completed within 72 hours.

**Requests analysis and approval rates**

Analysis revealed high approval rates of the funding requests. Throughout the process, as
many as 80.2% of requests were approved after first application form was submitted (Table 2). Specifically, 84% of the first-time requests and 76% of continuation requests for ranibizumab treatment were approved after first application form. Moreover, even after rejection, 14% of all requests were approved after resubmissions of amended application form. Eventually, solely 808 requests (5.7% out of all requests) were rejected. Out of these, 288 requests (5.1% out of first-time requests) were rejected, thus did not receive any funding of the treatment, while 520 continuation requests were denied, thus these patients' treatment funding was terminated. Ultimately, 13,278 requests for subsidization were approved (average 2.35 approved requests per patient).

De facto, during the study period nearly 99.8% of approved requests received the series of three injections. According to a report of Clalit Health Services, as many as 41,739 injections were supplied to the retina units at any of the 20 public hospitals in Israel. A diagnosis-based analysis reveals that the most frequent indication for treatment was AMD (61%), followed by DME (24%) and the rest had a complex diagnosis, CRVO/BRVO or miscellaneous (Table 1). The approval rate for requests differed significantly by indication (P < 0.001): 85%, 88%, 87%, 0% for AMD, DME, CRVO/BRVO and miscellaneous diagnoses, respectively. We further excluded patients with miscellaneous diagnoses, due to inadequacy to relevant indications. However, the likelihood of approval was lower for patients with AMD (OR 0.91, 95% CI 0.88-0.93), than for patients with DME (OR 1.27, 95% CI 1.77-1.37) or CRVO (OR 1.39, 95% CI 1.20-1.59), when compared to the rest of the diagnoses.

Overall, this process enabled treating about 18,000 patients with retinal disease effectively. While most of the patients received the less expensive, but not less effective treatment, only a reduced number of nonresponders were determined as appropriate for funding with almost 10 times costlier treatment.
Discussion

Ideally, comprehensive health coverage should be affordable, accessible, and appropriate. Here, we described a prior authorization program intended to effectively allocate a costly treatment, while maintaining a budgetary framework. A steering committee of experts determined the criteria for drug authorization according to evidence-based knowledge accumulated in the literature, and an ophthalmic specialists team approved or rejected applications submitted by fellow ophthalmologists. For first-time funding requests, the ophthalmic specialists team determined whether a patient, who applied for funding of ranibizumab, failed to respond to first-line bevacizumab, and matched the criteria for switching the treatment. For continuation of funding requests, treating ophthalmologists were required to prove that ranibizumab was effective or superior to previous bevacizumab treatment in the individual patient.

Our analysis showed that of the approximately 18,000 bevacizumab-treated members of Clalit Mushlam, 5,642 (31%) requested funding of second-line treatment with ranibizumab owing to lack of sufficient improvement or an adverse reaction to bevacizumab. Approval was ultimately granted to 95% of the patients, while 5% of the requests were eventually rejected. A similar overall rejection rate of 4.4% was described in an earlier analysis of a prior authorization program for a non-ophthalmic medications in a Medicaid HMO. Another study described the prior-authorization program for cyclooxygenase-2 inhibitors relative to nonselective nonsteroidal anti-inflammatory drugs, which resulted in a decrease in prescription rate of the costlier drug. However, in their restriction of cyclooxygenase-2 inhibitors, not all the programs considered its lower rates of gastrointestinal complications or other evidence-based criteria. Thus, in the absence of individual patient data, the clinical appropriateness of the prior authorization programs could not be determined.
To the best of our knowledge, gatekeeping rests mainly on the shoulders of primary physicians. This is because this role is unparented, even in the sensitive field of retina care. Given that primary physician gatekeeping can reduce healthcare costs by a reported 15-26%, we might expect a similar decrease, in case peers within the same medical field authorize procedures and medications according to pre-set clinical criteria.

The clinical criteria for the approval of ranibizumab use under Clalit Mushlam were continuously updated during the study period. The prospective accumulation of such a large body of individual patients' data is invaluable for future assessments of the clinical benefit of second-line ranibizumab in patients with retinal disease, in addition to the clinical benefit of a prior-authorization policy itself. Although several studies have investigated the economic savings and reduction in medication use following prior authorization in Medicaid programs, none addressed their clinical benefit yet.

The requirements for clinical appropriateness varied among the approval procedures of the different states, and none of the studies had access to patient data.

The high approval rate of requests (94.3%) might be due to accurate adaptation of the guidelines for ranibizumab treatment and careful selection of cases for submission by the treating ophthalmologists, knowing that their requests are going to be inspected by their peers.

The reason for approval rate of 84% of the first-time requests, compared to the approval rate of 76% of continuation requests, might originate from two possibilities: this might be associated to the higher adherence rate of physicians to their prior recommendations despite the absence of benefit evidence, hoping for improvement; this might be due to the higher threshold of criteria for ranibizumab treatment continuation, rather than initiation. These should be further investigated.

In our cohort, 99.8% of the patients approved for ranibizumab treatment actually received
the injections. This finding suggests that co-payment did not deter treatment and emphasizes the necessity of the treatment also in the opinion of these patients.

The number of 41,739 ranibizumab injections that were supplied to the retina units during the research period was higher than the expected 39,834 injections (13,278 approved funding requests, times 3 injections per approval). The reason for that was mainly because requests for two eyes of the same patient were submitted on the same application form, and thus were counted as one approved request.

Eventually the average number of injected ranibizumab vials was 10,888 annually, while the number expected by the steering committee was ~16,000. The reasons for that gap may be due to several reasons: (i) the estimation by the steering committee may have been overly cautious, (ii) intervals between injections may have increased due to stable improvement of the retinal state, and (iii) the retina units may have had a limited capability to treat such a large quantity of patients.

We believe that the inclusion of funding of such a novel treatment as ranibizumab to Clalit Mushlam could have potentially ended in switch of treatment in the vast majority of the ~18,000 bevacizumab-treated members of Clalit Mushlam, without implementing the prior authorization mechanism. Hypothetically, taking into consideration both a ~$1,000 gap per injection between the costlier ranibizumab and bevacizumab, and 900 preventions of patients' treatment switching (5% of ~18,000 patients), ~2.5 million dollars were potentially saved without substantially affecting patient outcomes. Similar assumptions and saving out of forecast model were predicted in switching to less expensive "blindness drug". (31)

Additionally, the possibility that successful outcomes of treatment may cause the increase of incoming requests should be taken into account.

The paper is not without limitations, One limitation of the present report is the non-
uniform dispersion of indications for ranibizumab treatment throughout the study period. The changing available literature, pointing to new avenues of treatments, leads to the need for flexibility in such program. Second, we relied on the Clalit Health Services report, which rounded, and might miscounted, the number of bevacizumab-treated patients.

Conclusion

We describe prior authorization program for a costly and an effective medication for retinal diseases, as a replacement for a cheaper treatment, in case of the latter's failure. This was enabled by a careful selection of patients by ophthalmologists determined criteria for the funding of almost a 10-times costlier treatment. This approach enabled treatment for thousands of patients under professionally accepted clinical considerations, within a framework budget.

Lastly, owing to the clinical considerations that exist in this process, it is an integral part to assess not only its economic, but also its clinical benefits. We aim to further collect the data and investigate the clinical aspects of this intervention.

Declarations

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**Authors' contributions:**

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Irit Rosenblatt – Study Design and paper review

, Idan Hekselman – Statistical analysis

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If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.

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Legends

FIGURE 1 (Request form)
Caption: Clalit Mushlam application form for second line Ranibizumab treatment funding
SOURCE: [Authors’ translation of Clalit Mushlam application form).

FIGURE 2
Caption: Ranibizumab funding request process flowchart
Source: [Authors’ visual representation of Clalit Mushlam’s algorithm for ranibizumab funding process)

TABLE 1
Caption: Inquiries and approvals for Ranibizumab according to the type of retinal disease, age and gender.
Source: [Authors’ analysis of data from Clalit Mushlams’ cohort of members funding applications, March 1, 2012 to December 31, 2015.]

FIGURE 3
Caption: Monthly requests submission rate
Source: [Authors’ analysis of data from Clalit Mushlams’ cohort of members funding applications, March 1, 2012 to December 31, 2015.]

TABLE 2
Caption: Summary of patients’ requests for funding of Ranibizumab
Source: [Authors’ analysis of data from Clalit Mushlams’ cohort of members funding
applications, March 1, 2012 to December 31, 2015.]

Figures
Figure 1

(Request form) Clalit Mushlam application form for second line Ranibizumab treatment funding SOURCE: (Authors’ translation of Clalit Mushlam application form).
Figure 2
Ranibizumab funding request process flowchart

Source: [Authors' visual]
Figure 3

Monthly requests submission rate

Source: [Authors’ analysis of data from Clalit Mushlams’ cohort of members funding applications, March 1, 2012 to December 31, 2015.]

Supplementary Files

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Table 1.pdf
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