Older Drugs With Limited Trial Evidence: Are They Worth the Expense? The Case of Repository Corticotropin Marketed as H.P. Acthar Gel

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Over the past decade, substantial increases in the prices of older drugs, such as insulin, penicillamine, pyrimethamine, and repository corticotropin (rACTH), have generated controversy. However, compared with the others, rACTH—better known by its brand name, H.P. Acthar gel—has little evidence supporting its use, and the availability of cheaper alternatives, such as prednisone, makes its case worth reviewing.

Repository corticotropin was developed as a by-product of the meatpacking industry by Armour & Company in the late 1940s. It was approved by the U.S. Food and Drug Administration (FDA) in 1952 for treating inflammatory conditions after Hench and other researchers at the Mayo Clinic showed that rACTH and cortisone were beneficial and safe for rheumatoid arthritis (1, 2). The rights to rACTH were transferred from Armour to Rhône-Poulenc, which became Aventis and later merged with Sanofi (**Figure**). After the development of prednisone and other synthetic steroids in the 1980s, demand for rACTH decreased. It was practically forgotten in adult medicine but continued to be used for treatment of infantile spasms. In 2001, Questcor acquired rACTH and increased its price from $40 to $700 per vial. In 2007, the cost was increased from an average wholesale price of $2062 per vial to an estimated $23 000 (3, 4).

Questcor began marketing rACTH for other indications and, after identifying rheumatology as the largest market opportunity, increased its rheumatology sales force by 5-fold (5). Indications aside from infantile spasms included exacerbations of multiple sclerosis in adults and the umbrella term "rheumatic, collagen, dermatologic, allergic states, ophthalmic, respiratory, and edematous state" [sic]. The drug has been specifically marketed for rheumatologic indications, including inflammatory myopathies, rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus, and symptomatic sarcoidosis (2). As a result, rheumatology is currently the specialty with the most rACTH prescribers in the Medicare program (6). Questcor also bought Synacthen, the main competitor to rACTH, thus becoming the only manufacturer and effectively creating a monopoly on rACTH in the United States (3). Mallinckrodt Pharmaceuticals acquired Questcor in 2014, and rACTH currently costs $40 000 per vial (3).

The FDA approved rACTH before the need for randomized trial evidence showing efficacy; the only requirement at the time was to demonstrate safety (7). Because rACTH had already been approved for several conditions, there was little incentive to perform additional trials. The low quality of the evidence supporting use of rACTH compared with most prescription medications used in rheumatology makes its role in the treatment of inflammatory diseases unclear. For example, in rheumatoid arthritis, one of the most prevalent inflammatory conditions, only case reports or small case series of rACTH have been published since the observations of Hench and colleagues (1). This lack of evidence is similar for other conditions, including psoriatic arthritis, systemic lupus erythematosus, and dermatomyositis. Perhaps more important, for adult indications there is little evidence that rACTH is superior to or causes fewer adverse effects than the cheaper synthetic corticosteroids (prednisone has an average cost of $40 per year). Studies of the comparative effectiveness and safety of rACTH and prednisone have not been done.

Despite the lack of evidence, use of rACTH has resulted in a substantial cost burden to Medicare. In 2015, the Centers for Medicare & Medicaid Services (CMS) paid more than $500 million for the drug, an amount that had increased steadily since 2012 (6). According to the CMS Dashboard, in 2017 rACTH was the 44th most expensive drug in the Medicare program despite being used by only about 2800 beneficiaries (8). Furthermore, taxpayers are shouldering the cost burden to a greater degree than private insurers. Aetna, Cigna, and UnitedHealthcare have restricted reimbursement for rACTH in recent years, citing its lack of proven efficacy and the availability of more affordable options. Medicare continues to pay for it because CMS provides reimbursement for any FDA-approved medication that is determined to be a covered Medicare Part D drug—a criterion that rACTH meets (9).

If clinical decisions are to be based on the principles of evidence-based medicine, researchers need to generate high-quality evidence that will guide clinicians, patients, and other stakeholders about the role rACTH may play in treatment of rheumatologic disease. Mallinckrodt has stated that among its priorities are to expand the evidence base for rACTH and to differentiate it from currently available glucocorticoids (10). Several clinical trials of rACTH for rheumatic conditions are registered at ClinicalTrials.gov; however, they are predominantly small, open-label trials, and few have a placebo comparison group. None of these trials will provide evidence for effectiveness of rACTH over synthetic glucocorticoids because they do not include an active comparator.

High-quality randomized, double-blind, controlled trials are needed to evaluate the comparative effectiveness and safety of prednisone or other glucocorticoids and rACTH. Further, the cortisol equivalent of various rACTH doses should be assessed in vivo to understand the biological activity as well as dose equivalency between rACTH and currently available glucocorticoids.

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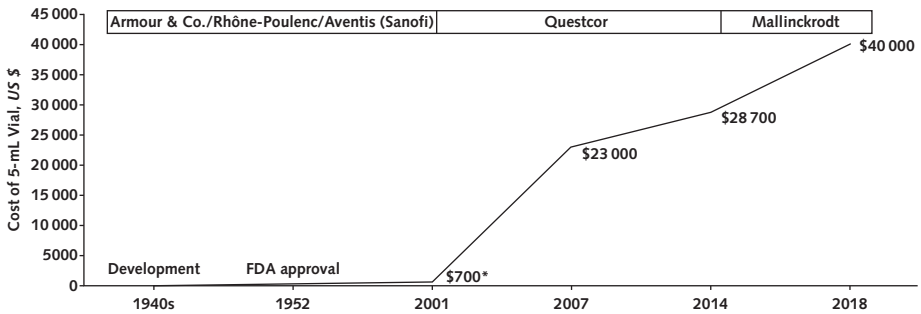
Figure. Timeline of changes in ownership and price of repository corticotropin since development.



FDA = U.S. Food and Drug Administration.
* Price per vial was ≤$50 before 2001.

Trials comparing rACTH with placebo or single-group trials will not add new knowledge. Notwithstanding the financial burden on CMS and other consumers, without evidence of the safety and effectiveness of rACTH compared with other glucocorticoids, clinical use is wasteful. This case study argues for government funding of clinical trials of rACTH as a potential solution for this conundrum. Obtaining more data on the comparative effectiveness and safety of this drug in the treatment of rheumatologic conditions is clearly in the best interest of Medicare beneficiaries and taxpayers.

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