Efficacy and safety of adalimumab in Crohn's disease

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Therapeutic Advances in Gastroenterology
(2008) 1(1) 43–50
DOI: 10.1177/1756283X08092548

***Abstract*:** Adalimumab (ADA) is a subcutaneously (SC) self-administered fully human Ig G1 monoclonal antibody directed against tumor necrosis factor alpha (TNFα). In the CLASSIC I dose-ranging trial, ADA was superior to placebo for inducing remission in patients with moderate-to-severe Crohn's disease (CD) naive to TNFα inhibitor therapy. In CLASSIC II, patients in remission following CLASSIC I maintained remission for up to 56 weeks while on ADA. In CHARM, approximately 40% of the 499 patients with moderate-to-severe CD who responded to ADA, maintained remission at 26 and 52 weeks, thus confirming long-term efficacy. ADA demonstrated steroid-sparing properties, beneficial effects in patients with perianal fistulas, and decreases in rates of hospitalization and surgery. Sub-group analyses demonstrated similar remission rates irrespective of concomitant immunosuppressive use or previous exposure to other TNFα inhibitor therapy. In the GAIN trial, 325 patients who had either lost response or become intolerant to infliximab (IFX) were randomized to recieve ADA induction therapy or placebo. In this difficult-to-treat patient population, 21% achieved remission and half demonstrated clinical benefit from ADA induction therapy. Injection site reactions may occur with SC ADA (2–5% of patients), which are generally less dramatic in nature than infusion reactions experienced with intravenous IFX. Immunogenicity occurs with all monoclonal antibodies; however, in the CD development program anti-ADA antibodies were detected at low rates (0.7 and 2.6% of patients in the CLASSIC I and CLASSIC II studies, respectively). Based on robust short- and long-term efficacy data from large randomized controlled trials and a favorable safety signal, ADA has become a key addition to the therapeutic armamentarium in the treatment of moderate-to-severe CD.

***Keywords*:** Crohn's disease, TNFα inhibitors, adalimumab, infliximab

Introduction

Adalimumab (Humira^{TM}) is a subcutaneously (SC) self-administered recombinant fully-human monoclonal immunoglobulin (IgG1) antibody. It binds with a high affinity and specificity to soluble tumor necrosis factor (TNFα) and neutralizes its biological function by blocking its interaction with TNF receptors [Sorbera *et al*. 2001]. Given the central role of TNF in the inflammatory cascade, adalimumab has potential benefit in a plethora of inflammatory and immune-mediated disorders. The SC route of administration offers patients the additional benefit of convenience since medication administration can be done without travel to an infusion center thus offering patients the opportunity to avoid missing time off from work or schooling for infusion (when compared to infliximab).

Infliximab was the first TNFα inhibitor approved for the treatment of Crohn's disease (CD) in the US and other global jurisdictions. Similar to infliximab, adalimumab has been evaluated for its effect in inducing and maintaining remission, its steroid-sparing effect, and its impact on hospitalizations and surgeries. However, in addition, adalimumab offers a significant treatment option in patients who have lost response to or become intolerant to infliximab. This represents approximately one third of patients over the first year of infliximab therapy based on clinical trial data [Hanauer *et al*. 2002]. This brief review will highlight the evidence for adalimumab's efficacy in CD and also summarize safety data as well as cost implications. The use of other biologics in CD, including certolizumab pegol, has been reviewed elsewhere and is outside the scope of this review [Clark *et al*. 2007].

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Pharmacokinetics

The time to reach maximum concentration (T_{max}) for adalimumab is 131 ± 56 h (single 40 mg SC dose in healthy subjects) and the mean terminal elimination half life is 10–20 days [single intravenous (IV) dose in rheumatoid arthritis (RA) patients] [Abbott Laboratories, 2008]. By comparison, the median terminal half life of infliximab is 8–10 days [Remicade, 2007]. Onset of initial response in RA studies is from 24 h to 7 days, compared with 3–7 days for infliximab in RA and 1–2 weeks in CD (both drugs given IV) [Micromedex, 2008a,b]. Duration of response following single IV dosing in RA studies is up to 12 weeks, compared to 4–48 weeks for infliximab in CD (single IV dose) and 6–12 weeks in RA (multiple IV doses) [Micromedex, 2008a,b].

Efficacy of adalimumab in CD

The American Gastroenterological Association (AGA) produced a recent consensus document on the use of biologics in inflammatory bowel disease (IBD) and stated that infliximab and adalimumab have similar efficacy in the ability to induce response and remission in CD [Clark *et al*. 2007]. This conclusion was derived by comparing separate infliximab and adalimumab studies. There are no published head-to-head comparisons of the drugs. The authors also remarked that the clinical significance of differences such as route of administration (SC for adalimumab vs IV for infliximab) and immunogenicity is still unknown (see pharmacokinetics section).

The best evidence for the use of adalimumab in CD comes from three randomized controlled trials (RCTs). The CLASSIC (Clinical Assessment of Adalimumab Safety and Efficacy Studied as Induction Therapy in Crohn's Disease) I study comprised 299 patients with moderate-to-severe CD naive to previous TNFα inhibitor; CHARM (Crohn's trial of the fully Human antibody Adalimumab for Remission Maintenance) comprised 499 patients who received maintenance treatment for moderate to severely active CD; and GAIN (Gauging Adalimumab efficacy in Infliximab Non-responders) had 325 patients with moderate to severely active CD who had previously lost response or were unable to tolerate infliximab [Colombel *et al*. 2007c; Sandborn *et al*. 2007; Hanauer *et al*. 2006c].

Induction therapy

The CLASSIC I dose-ranging RCT comprised a total of 299 patients with moderate-to-severe CD naive to TNFα inhibitor therapy who were randomized to receive adalimumab (40/20 mg, 80/40 mg, or 160/80 mg) or placebo at weeks 0 and 2 [Hanauer *et al*. 2006c]. The primary endpoint was remission at week 4 defined by a CD activity index (CDAI) <150. The remission rates at week 4 (primary endpoint) in the adalimumab 40/20 mg, 80/40 mg, and 160/80 mg groups were 18% ($p = 0.36$), 24% ($p = 0.06$), and 36% ($p = 0.001$), respectively, and 12% in the placebo group. The authors concluded that adalimumab was superior to placebo for inducing remission in CD patients with moderate-to-severe disease who were naive to TNFα inhibitor therapy with the 160/80 mg having the most robust response. Response rates were also measured in this study. In the highest dosing group (160/80 mg), 50 and 59% of patients had a response defined by a 100-point and 70-point decrease in CDAI, respectively.

Maintenance therapy

There were 275 patients from CLASSIC I who were entered into the CLASSIC II trial [Sandborn *et al*. 2007]. They received open-label adalimumab 40 mg at weeks 0 (week 4 CLASSIC I) and at week 2. Patients who were in remission at both week 0 (end CLASSIC I/beginning CLASSIC II) and week 4 were re-randomized to 40 mg every other week (eow), weekly, or placebo through 56 weeks. In this re-randomized cohort of 55 patients, 79% who received adalimumab 40 mg eow and 83% who received 40 mg weekly maintained remission through week 56 (primary endpoint) compared with 44% for placebo ($p < 0.05$ for both adalimumab groups vs placebo). The patients from CLASSIC I who had not been in remission entered an open-label arm and received adalimumab 40 mg eow (dosages could be increased to 40 mg weekly if there was a nonresponse or flare). There were 204 patients in the open-label arm and 46% were in clinical remission at week 56. Thus, CLASSIC I and II showed that adalimumab induced and maintained clinical remission in patients with moderate-to-severe CD naive to TNFα inhibitor treatment.

In CHARM, 854 patients with moderate-to-severe CD received open-label adalimumab SC at doses of 80 mg at week 0 and 40 mg at week 2 (this dose was chosen before the results

of CLASSIC I were known) [Colombel *et al.* 2007c]. Patients who had been exposed to infliximab in the past and either lost response or had become intolerant to infliximab were eligible for this trial. Approximately 60% of patients responded at week 4 (identified by a drop in CDAI of 70 points) and were then randomized to one of three treatment arms: adalimumab 40 mg eow, adalimumab 40 mg weekly, or placebo. The primary study endpoints were clinical remission at weeks 26 and 56 amongst responders. At week 26, 40% of the adalimumab 40 mg eow, 47% of the adalimumab 40 mg weekly and 17% of the placebo groups were in remission ($p = 0.001$ for both groups compared to placebo, no difference between active groups). This benefit was maintained out to week 56 with 36% adalimumab 40 mg eow, 41% adalimumab 40 mg weekly, and 12% placebo groups remaining in remission ($p = 0.001$). There was no difference in the proportion of patients who were able to maintain remission or response according to their previous infliximab exposure.

An abstract presented at the American College of Gastroenterology (ACG) 2006 meeting of a subgroup analyses from CHARM showed that adalimumab demonstrated steroid-sparing efficacy comparable to that reported for infliximab [Hanauer *et al.* 2006b]. Corticosteroid dosages were tapered at week 8 in selected patients who were in clinical remission. At week 56, steroid-free remission (for at least 90 days) was significantly greater among patients receiving adalimumab maintenance therapy than those receiving placebo (29% vs 5%).

Within the CHARM study population, 117 patients had active perianal fistulizing disease. Although, the study was not specifically designed or powered to evaluate patients with fistula, one third of patients treated with adalimumab had complete and maintained healing of fistula. Results of a 12-month, open-label extension study from CHARM that assessed long-term efficacy at fistula healing (100% closure) and response (≥50% closure) were presented at ACG in 2007 [Colombel *et al.* 2007a]. Adalimumab patients who enrolled in the extension study had baseline fistulas in CHARM and were still blinded to receive open-label adalimumab therapy. Pooled data from the two adalimumab doses showed that 70 patients met the study criteria. Fistula healing rates from the start of CHARM were 50% (6 and 12 months), 56% (18 months), and 60% (24 months), while fistula response rates were 64% (6 months), 59% (12 months), and 71% (18 and 24 months). A separate analysis of the extension study showed that of the 40 patients with healed fistulas at the end of CHARM, healing persisted in 79% at 6 months and 76% at 12 months, while response occurred in 87% at 6 months and 79% at 12 months (assumes nonresponse among those patients lost to follow-up).

Previous TNFα inhibitor therapy

Several small trials have suggested that adalimumab may be effective in patients who have lost response or become intolerant to infliximab [Ho *et al.* 2008; Hinojosa *et al.* 2007; Peyrin-Biroulet *et al.* 2007; Seiderer *et al.* 2007; Papadakis *et al.* 2005; Sandborn *et al.* 2004; Youdim *et al.* 2004]. Further findings from CHARM presented at the ACG 2006 meeting showed that adalimumab was effective in sustaining clinical remission in CD regardless of concomitant immunosuppressant therapy or history of TNFα inhibitor therapy [Hanauer *et al.* 2006a]. This issue was addressed in the GAIN study, a placebo-controlled RCT in 325 patients with moderate-to-severe CD who had failed infliximab therapy (i.e., intolerant of infliximab or must have previously responded then lost response to infliximab) [Sandborn *et al.* 2007a]. Patients were treated with adalimumab (160 mg at week 0 then 80 mg at week 2) or placebo. At week 4, of the 301 patients who completed the trial, induction of remission (primary endpoint) was greater for adalimumab than for placebo (21% vs 7%, $p < 0.001$).

Safety

Adalimumab was well tolerated in the efficacy-based RCTs reported earlier. An analysis of an open-label extension study of over 1100 CD patients from the CHARM and GAIN studies presented at the ACG in 2007 showed the safety profile of adalimumab was similar to its safety profile in other conditions and similar to infliximab in CD [Colombel *et al.* 2007b]. Serious adverse events were reported in 25% of patients, injection-site reactions in 20%, malignant neoplasms (1.7%), opportunistic infections (2.1%), tuberculosis (TB) (0.2%). More extensive safety data for adalimumab in CD is relatively lacking compared to efficacy data; therefore, this section will look at safety of TNFα inhibitors in general. The AGA stated that all TNFα inhibitors have similar safety profiles

[Clark *et al*. 2007]. They increase the risks of infections, such as TB. Infusion and injection site reactions occur with all TNFα inhibitors, although rates vary by mode of administration [Clark *et al*. 2007].

Injection site reactions and immune response

SC adalimumab can be associated with injection site reactions. In the CHARM trial, injection site reactions occurred in 2% of patients during induction and in up to 4.8% of those treated with the 40 mg weekly maintenance regimen [Colombel *et al*. 2007c]. Irritation and pain at the injection site were reported by over 4% of patients during induction.

Antibody formation against biologic therapies is common. Their formation may be related to an increased risk of infusion reactions but it is not possible to predict this on an individual basis. Also, it is possible that antibodies will attenuate the degree and duration of response [Clark *et al*. 2007]. The fact that adalimumab is not comprised of nonhuman or artificial sequences suggests it should have a low potential for immunogenicity [Sorbera *et al*. 2001]. There were 0.7% of patients in CLASSIC I and 2.6% in CLASSIC II who developed anti-adalimumab antibodies [Sandborn *et al*. 2007; Hanauer *et al*. 2006c).

Autoimmune disease

The development of autoantibodies is common with TNFα inhibitor therapy; however, its clinical relevance is uncertain. It does not appear to reduce the efficacy of TNFα inhibitor therapy (i.e., in contrast to the development of antibodies against the actual biologic drug). Serologic evidence of autoimmunity appears to be less with adalimumab than with infliximab [Clark *et al*. 2007] though direct comparison is lacking. Respective product information states that about 12% of adalimumab-treated patients developed positive antinuclear antibodies (ANA) compared with 7% of placebo-treated patients [Abbott Laboratories, 2008] – this compares with about 50 and 20% for infliximab vs placebo-treated patients [Remicade, 2007]. In the CLASSIC II trial 33 of 172 patients (19%) developed ANA antibodies. Anti-dsDNA antibodies in a juvenile idiopathic arthritis trial were found in 10% of adalimumab-treated patients [Abbott Laboratories, 2008]. Approximately, 20% of infliximab-treated patients produced anti-dsDNA antibodies (direct comparison is difficult across different studies) [Remicade, 2007]. The absolute incidence of systemic lupus erythematosus with infliximab was reported as 0.19% in one survey [De Brandt *et al*. 2005]. A recent review analyzed the association of autoimmune diseases with use of TNFα inhibitor therapy [Ramos-Casals *et al*. 2007]. The MEDLINE search revealed 233 cases of autoimmune diseases (vasculitis in 113, lupus in 92, interstitial lung diseases in 24, and other diseases in 4) secondary to TNFα inhibitor therapy in 226 patients [the agents were given for RA in 187 (83%) patients, CD in 17, ankylosing spondylitis in 7, psoriatic arthritis 6, juvenile RA in 5, and other diseases in 3. Infliximab was the biologic drug in 105 patients, etanercept in 96, and adalimumab in 21].

Malignancy

TNFα inhibitors may predispose patients to an increased risk of malignancies or accelerate their development. Caution is advised when prescribing TNFα inhibitors in patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.

A meta-analysis of infliximab or adalimumab studies in RA, found that malignancies developed in 29 of 3192 (0.9%) patients treated with infliximab or adalimumab, compared with 3 of 1428 (0.2%) patients given placebo [Bongartz *et al*. 2006]. Caution should be exercised when interpreting this data since the incidence of malignancies were not normalized to the patient years of follow-up. Also, many of the malignancies were nonmelanotic skin cancers. The risk of malignancies was not different from placebo with low dose TNFα inhibitors but was 4-fold greater with high doses of infliximab or adalimumab. A pooled odds ratio (OR) for malignancy following TNFα inhibitor therapy of 3.3 [95% confidence interval (CI) 1.2–9.1] was calculated. The number needed to harm was 154 (95% CI 91–500) for one additional malignancy within a treatment period of 6–12 months. The authors concluded there is evidence of a dose-dependent increased risk of malignancies in patients with RA treated with TNFα inhibitors. Similar results were reported in a recent American College of Physicians (ACP) Journal Club analysis [ACP, 2006]. It found that the malignancy risk was greater in RA patients receiving a high dose of TNFα inhibitors compared with placebo (OR 4.3, 95% CI 1.6–12) than in those receiving a low dose (OR 1.4, 95% CI 0.3–5.7).

Direct comparison of high and low dose also showed increased risk for malignancy with high-dose treatment (OR 3.4, 95% CI 1.4–8.2).

Infection

The AGA guidelines state that US postmarketing surveillance data among patients with RA indicated similar rates of TB with different TNFα inhibitors. A broad range of other infections have been reported with infliximab and adalimumab. The reported serious infection rates for infliximab were approximately 4% in the ACCENT I and II trials [Sands *et al.* 2004; Hanauer *et al.* 2002] whilst 3.6% was reported for adalimumab administered every other week in the CHARM trial [Colombel *et al.* 2007c]. The ACP Journal Club meta-analysis found serious infection risk with TNFα inhibitors was increased in patients with RA [ACP, 2006]. A dose effect was not observed for serious infection (high dose vs low dose, OR 1.4, 95% CI 1.0–2.0). The meta-analysis by Bongartz *et al.* showed a 2-fold increased risk of serious infections with TNFα inhibitors, regardless of dose [Bongartz *et al.* 2006]. The number needed to harm was 59 (95% CI, 39–125) for one serious infection within a treatment period of 3–12 months. The authors concluded there is evidence of an increased risk of serious infections in patients with RA treated with TNFα inhibitors. Caution should be exercised in interpreting this data given that multivariate logistic regression analysis was not performed.

Adalimumab was well tolerated in CHARM, and its safety profile was consistent with that reported in previous studies with adalimumab and other TNFα inhibitors [Colombel *et al.* 2007c]. The rate of infections was similar across all three treatment arms. The ACG report stated that there was one case of TB in each of the adalimumab groups, and none in the placebo patients [Plevy, 2006].

Neurologic disorders

Optic neuritis, seizure, and new onset or exacerbation of central nervous system demyelinating disorders (includes multiple sclerosis), have been reported rarely with the use of TNFα inhibitors. The majority of these cases were reported with infliximab use, probably because of greater patient exposures [Clark *et al.* 2007]. Two cases of optic neuritis associated with adalimumab therapy has recently been reported [Chung *et al.* 2006]. TNFα inhibitors should not be used in patients with known demyelinating disease.

Use in specific age groups

There are no studies of adalimumab in pregnant women; therefore, its use in pregnancy is recommended only if clearly needed. There are no studies of adalimumab in children with CD [Clark *et al.* 2007]. There are two cases of its use in refractory CD in children [Hadziselimovic, 2008; Mian and Baron, 2005].

With regard to older patients, there were over 500 RA patients 65 years or over, including 107 patients $\geq$ 75 years, who received adalimumab in clinical studies. There was no overall difference in effectiveness between these subjects and younger subjects. The frequency of serious infection and malignancy among adalimumab-treated subjects over age 65 was higher than for those under age 65. Because there is a higher incidence of infections and malignancies in the elderly population in general, caution should be used when treating the elderly.

Cost

When weighing the risks and benefits of biologic therapy for patients with IBD, physicians must account for the consequences of undertreated IBD. These include the direct costs of hospitalizations and operations for IBD, the direct costs of treatment for side effects associated with chronic, nonbiologic therapies, and indirect costs associated with lost productivity or nonmonetary costs such as quality-of-life (QOL) decrements [Clark *et al.* 2007].

The inflammatory bowel disease questionnaire (IBDQ) is a validated measure of QOL in patients with IBD that assesses systemic features, bowel system, emotional and social function. Scores range from 32 to 224 with a score of >170 correlating with clinical remission (defined by a CDAI <150). In patients continued on adalimumab 40 mg SC eow or weekly in CLASSIC II, IBDQ >170 were maintained, whereas it rapidly declined in patients on placebo, demonstrating that sustained response to adalimumab was associated with improved QOL [Rutgeerts *et al.* 2006]. In the GAIN study, scores in adalimumab-treated patients were significantly higher in all four domains of the IBDQ than in placebo-treated patients again demonstrating

Table 1. Summary of American Gastroenterological Association (AGA) consensus on the use of adalimumab in Crohn's disease (CD).

Use	Notes (grading)
Induction of response	In adult or children outpatients with moderate-to-severe CD who have failed therapy with and are treated concomitantly with aminosalicylates, antibiotics, corticosteroids, or immunosuppressants (A, adults; C, children)
Induction of remission	In adult or child outpatients with moderate-to-severe CD who have failed therapy with and are treated concomitantly with aminosalicylates, antibiotics, corticosteroids, or immunosuppressants (A, adults; C, children)
Maintenance of response after adalimumab	Adults (A), children (C)
Maintenance of remission after adalimumab	Adults (A), children (C)
Loss of response or intolerance to infliximab	Absolute response rate may be lower than in TNFα inhibitor naïve patients (A)
Induction of response in adult outpatients with draining perianal fistulas	Adults who have failed therapy with and are treated concomitantly with aminosalicylates, antibiotics, corticosteroids, or immunosuppressants (C)

TNFα, tissue necrosis factor alpha.
Summarized and adapted from AGA guidelines [Clark *et al.* 2007]. Evidence was evaluated using the Oxford criteria that grades individual studies according to study design and strength of results (A = highest quality, D = poor quality). Note that adalimumab use in children with CD is not an FDA-approved indication.

improved QOL with treatment with adalimumab [Sandborn *et al.* 2007a].

A UK study stated that only a minority of CD and ulcerative colitis sufferers are hospital inpatients but they account for approximately half the direct medical costs of inflammatory bowel disease (IBD) treatment. Drug costs contributed less than a quarter of the total healthcare costs [Luces and Bodger, 2006]. Lifetime costs for IBD are comparable to a number of major diseases, including heart disease and cancer. The authors stated that in the next 5–10 years, the contribution of drug costs will increase as biologic therapies become more widely used. The key economic question is whether the health gains from these drugs will lead to reduced expenditures on hospitalization and surgery.

In a study evaluating patients enrolled in the CHARM study, a secondary analysis evaluated rates of hospitalization in patients treated with placebo vs those treated with adalimumab [Feagan *et al.* 2007b]. At 56 weeks, the actuarial hospitalization rate in placebo and adalimumab-treated patients was 13.9% and 5.9%, respectively ($p < 0.01$) – treatment with adalimumab was the only independent factor associated with reduced risk.

One study looked at the effect of infliximab maintenance treatment on hospitalizations, surgeries and procedures among 282 patients (195 responders) with fistulizing CD who were in the ACCENT II study [Lichtenstein *et al.* 2005]. Patients randomized as responders and receiving infliximab maintenance showed significant improvements over those receiving placebo maintenance. They had significantly less days of hospitalization (0.5 vs 2.5 days; $p < 0.05$), mean numbers per 100 patients of hospitalizations (11 vs 31; $p < 0.05$), all surgeries and procedures (65 vs 126; $p < 0.05$), inpatient surgeries and procedures (7 vs 41; $p < 0.01$), and major surgeries (2 vs 11; $p < 0.05$). Reduced hospitalization has also been reported for patients in remission with CD and in patients given scheduled infliximab therapy [Rutgeerts *et al.* 2006; Lichtenstein *et al.* 2004; Rutgeerts *et al.* 2004]. A report presented at the ACG in 2007 concluded that maintenance therapy with infliximab reduced hospitalizations and surgeries in patients with CD when compared with episodic infliximab therapy [Thompson *et al.* 2007].

Another ACG presentation consisted of an analysis of a managed care database containing 9811 CD patients who had either continued or discontinued corticosteroid usage [Feagan *et al.* 2007a]. Costs related to CD and total costs were significantly higher among patients on steroids compared to those who were not taking steroids ($US5270 vs $US3275 and $US10786 vs $US7759, respectively). Thus, savings on steroid use need to be considered when looking at the overall cost of CD treatments that enable discontinuation of steroids.

Conclusions

Treatment with TNFα inhibitors has been a significant advance in the treatment of IBD. Adalimumab, a fully human, monoclonal antibody can be self-administered every week to every other week and has demonstrated efficacy and safety for induction of remission and thus treatment of patients with CD. Adalimumab every other week additionally maintains remission, reduces hospitalizations, allows for withdrawal of steroids, and improves quality of life. Table 1 shows the latest AGA recommendations on its use. The ease of administration, sustainability, and convenience of adalimumab make this an attractive therapeutic agent for treatment of patients with CD.

Acknowledgements

Parts of this manuscript were prepared while GM was employed by the New South Wales Therapeutic Advisory Group, St Vincent's hospital, Sydney, Australia.

Conflict of interest statement

The authors declare the following potential conflict of interest. Gary Lichtenstein has received research funding and honoraria from Abbott, Centocor, Elan, Bristol Myers Squibb, and UCB. Remo Panaccione has received research funding and honoraria from Abbott, Contocor, Elan, Bristol Myers Squibb, Schering Plough and UCB.

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