Research Paper

Age-related trends in injection site reaction incidence induced by the tumor necrosis factor-α (TNF-α) inhibitors etanercept and adalimumab: the Food and Drug Administration adverse event reporting system, 2004–2015

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Abstract

Tumor necrosis factor-α (TNF-α) inhibitors are increasingly being used as treatment for rheumatoid arthritis (RA). However, the administration of these drugs carries the risk of inducing injection site reaction (ISR). ISR gives rise to patient stress, nervousness, and a decrease in quality of life (QoL). In order to alleviate pain and other symptoms, early countermeasures must be taken against this adverse event. In order to improve understanding of the risk factors contributing to the induction of ISR, we evaluated the association between TNF-α inhibitors and ISR by applying a logistic regression model to age-stratified data obtained from the Food and Drug Administration Adverse Event Reporting System (FAERS) database.

The FAERS database contains 7,561,154 reports from January 2004 to December 2015. Adjusted reporting odds ratios (RORs) (95% Confidence Intervals) were obtained for interaction terms for age-stratified groups treated with etanercept (ETN) and adalimumab (ADA). The adjusted RORs for ETN*≥ 70 and ADA*≥ 70 groups were the lowest among the age-stratified groups undergoing the respective monotherapies. Furthermore, we found that crude RORs for ETN + methotrexate (MTX) combination therapy and ADA + MTX combination therapy were lower than those for the respective monotherapies.

This study was the first to evaluate the relationship between aging and ISR using the FAERS database.

Key words: etanercept, adalimumab, injection site reaction, adverse event reporting system.

Introduction

The treatment of rheumatoid arthritis (RA) and other immune-mediated diseases has benefited from the development of a variety of tumor necrosis factor-α (TNF-α) inhibitors such as etanercept (ETN), adalimumab (ADA), golimumab (GLM), certolizumab (CZM), and infliximab (INF)[1–6]. These TNF-α inhibitors are effective in reducing the signs and symptoms of RA and in inhibiting structural
damage compared to traditional disease-modifying anti-rheumatic drugs[7, 8]. ETN, ADA, GLM, CZM, and INF are currently available the U.S. Food and Drug Administration (FDA)-approved TNF-α inhibitors[1–6]. They all appear to possess similar efficacy in clinical practice. ETN, ADA, GLM, and CZM are administered subcutaneously (SC) by the patient. INF, on the other hand, is administered intravenously (IV) by a health care professional.

Patient experience with injectable biologics appears to be an important consideration when selecting a TNF-α inhibitor[9]. Several studies have found that patients prefer SC injection over IV drug administration and prefer to receive treatment at home[10, 11]. The adverse events reported in clinical trials of SC TNF-α inhibitors include injection site reactions (ISRs), infections, headaches, etc. ISR, by definition, includes any of the following: erythema, pruritus, pain, inflammation, rash, induration, itching, and edema. The prevalence of these symptoms has been reported as ranging from 12–37% in clinical trials[2, 3]. Since ISR is often subjective, and may not be a part of routine inquiries by physicians, its prevalence could be underestimated in many rheumatological practices[12]. Although SC TNF-α inhibitors may be more convenient than IV infusion, they may induce ISR, which may affect patient quality of life (QoL). ISR gives rise to stress, nervousness, and a reduced QoL. In order to alleviate pain and other symptoms, early countermeasures against this adverse event class must be taken. However, at present, even the prevalence and clinical importance of ISR in routine clinical practice is uncertain[13].

The FDA Adverse Event Reporting System (FAERS) is a spontaneous reporting system (SRS) and the largest and best-known database in world. Data collected from doctors, nurses, and other concerned clinical practitioners are compiled in this database. FAERS reflects the realities of clinical practice[14]. SRS can be used to evaluate drug-associated adverse events via disproportionality analysis, which usually involves the crude reporting odds ratio (ROR)[15]. The crude ROR can be used in a technique that allows for adjustments through logistic regression analyses in order to mitigate the effects of confounding factors[16–22].

To the best of our knowledge, the relationship between SC TNF-α inhibitors and ISR has not yet been evaluated with regards to age-stratified patient groups analyzed from SRS. In this study, we evaluated a possible relationship between SC TNF-α inhibitors and ISR from data available in the FAERS database using a logistic regression model and subset analysis. Furthermore, TNF-α inhibitors are often combined with methotrexate (MTX) in RA treatment[7, 8]. This combination therapy was found in our study to cause fewer ISR cases than monotherapy using a single TNF-α inhibitor.

**Methods**

Data from January 2004 to December 2015 present in the FAERS database were downloaded from the FDA website (http://www.fda.gov/). The FAERS database structure complies with standards of the International Council on Harmonization (ICH) E2B. DrugBank ver. 3.0 and 4.0 (The Metabolomics Innovation Centre, Canada, http://www.drugbank.ca/) were utilized as dictionaries for batch conversion and compilation of drug names[23]. We built a database that integrated the FAERS database and DrugBank data using FileMaker Pro 13 software (FileMaker, Inc.). In the FAERS database, adverse events are coded according to the terminology prescribed by the Medical Dictionary for Regulatory Activities (MedDRA) 19.0 (http://www.meddra.org/). The preferred terms (PTs) selected for identification of ISR reporting were 77 terms containing the words “injection site” (Table 1). We followed the FDA’s recommendation in adopting the most recent case numbers in order to identify duplicate reports from the same patient and exclude them from analysis[24]. Additionally, only reports with complete age and sex information were extracted.

From the selected reports, we calculated both the crude ROR and the adjusted ROR. Patients using TNF-α inhibitors were categorized by age (< 20, 20–29, 30–39, 40–49, 50–59, 60–69, and ≥ 70-year-old groups). Crude ROR was calculated using a two-by-two contingency table in the form of (a*d)/(b*c) (Table 2). A “case” was defined as patients reporting adverse events relating to “ISR”, while “non-cases” were defined as patients without adverse events relating to “ISR”[24]. RORs were each expressed as a point estimate with 95% confidence intervals (CIs). The safety signal was defined as the lower limit of the 95% CI for each ROR exceeding 1[15].

RORs can be adjusted using logistic regression analysis and then used to analyze the effects of interaction terms in detail[16–18, 21, 22]. The FAERS database included information relating to confounding factors that affect the crude ROR. The logistic model used to calculate the adjusted ROR was as follows:

\[
\log(\text{odds}) = \text{intercept} + \beta_1 Y + \beta_2 S + \beta_3 A + \beta_4 T + \beta_5 M + \beta_6 T*M + \beta_7 T*A
\]

\[(Y = \text{reporting year, } S = \text{sex, } A = \text{age-stratified group, } T = \text{TNF-α inhibitor, } M = \text{MTX})\]

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ADA-treatment subset. RORs of the ETN-treatment subset as well as the diseases[20, 25–27]. We evaluated the intra-class that are thought to share common risk factors and by limiting the analysis to a population of patients the effect of confounding factors on signal detection U.S.A.).

Because the FAERS database does not contain information on the severity of ISR, this information was not taken into account in our analysis.

**Table 1. Preferred terms associated with injection site reaction in MedDRA.**

| PT+CODE | PT NAME | PT+CODE | PT NAME |
|---------|---------|---------|---------|
| 10022044 | injection site abscess | 10064111 | injection site joint inflammation |
| 10022045 | injection site abscess sterile | 10053979 | injection site joint movement impairment |
| 10022046 | injection site anaesthesia | 10049261 | injection site joint pain |
| 10022048 | injection site atrophy | 10049260 | injection site joint swelling |
| 10022052 | injection site bruising | 10049262 | injection site joint warmth |
| 10054812 | injection site calcification | 10067253 | injection site laceration |
| 10050057 | injection site cellulitis | 10057665 | injection site lymphadenopathy |
| 10050082 | injection site coldness | 10067255 | injection site macule |
| 10022055 | injection site cyst | 10022081 | injection site mass |
| 10022056 | injection site dermatitis | 10056250 | injection site movement impairment |
| 10065600 | injection site discharge | 10022082 | injection site necrosis |
| 10051572 | injection site discolouration | 10022083 | injection site nerve damage |
| 10054266 | injection site discomfort | 10057880 | injection site nodule |
| 10067252 | injection site dryness | 10022085 | injection site oedema |
| 10069124 | injection site dysaesthesia | 10022086 | injection site pain |
| 10066422 | injection site eczema | 10066041 | injection site pallor |
| 10022059 | injection site erosion | 10066044 | injection site papule |
| 10022061 | injection site erythema | 10022088 | injection site paraesthesia |
| 10068689 | injection site exfoliation | 10022090 | injection site phlebitis |
| 10022062 | injection site extravasation | 10053396 | injection site photosensitivity reaction |
| 10022064 | injection site fibrosis | 10073174 | injection site plaque |
| 10022065 | injection site granuloma | 10022093 | injection site pruritus |
| 10022066 | injection site haematoma | 10054994 | injection site pustule |
| 10022067 | injection site haemorrhage | 10022094 | injection site rash |
| 10073418 | injection site hyperaesthesia | 10022095 | injection site reaction |
| 10022071 | injection site hypersensitivity | 10066797 | injection site recall reaction |
| 10073131 | injection site hypertrophic | 10066210 | injection site scar |
| 10022072 | injection site hypertrophy | 10059009 | injection site scar |
| 10074586 | injection site hypoaesthesia | 10066778 | injection site streaking |
| 10022075 | injection site induration | 10053425 | injection site swelling |
| 10022076 | injection site infection | 10022104 | injection site thrombosis |
| 10022078 | injection site inflammation | 10022103 | injection site ulcer |
| 10066083 | injection site injury | 10022107 | injection site urticaria |
| 10022079 | injection site irritation | 10067995 | injection site vasculitis |
| 10048648 | injection site ischaemia | 10022111 | injection site vesicles |
| 10074586 | injection site joint aches | 10066778 | injection site vasculitis |
| 10064949 | injection site joint discomfort | 10022112 | injection site warmth |
| 10064949 | injection site joint effusion | 10073752 | lack of injection site rotation |
| 10064949 | injection site joint effusion | 10073752 | lack of injection site rotation |
| 10076327 | injection site joint erythema | 10022478 | malabsorption from injection site |
| 10084111 | injection site joint inflammation | 10022478 | malabsorption from injection site |

a) Preferred Term

The 20–29-year-old group was used as a reference group to calculate RORs adjusted for age variations. A likelihood ratio test can be used to evaluate the effect of adding a particular term. Because the difference in -2 log-likelihood follows a chi-square distribution with one degree of freedom, adding an interaction term, in this case, was statistically significant (p < 0.05). These analyses were performed using JMP 11 (SAS Institute Inc., Cary, NC, U.S.A.).

The data subsets strategy may help to mitigate the effect of confounding factors on signal detection by limiting the analysis to a population of patients that are thought to share common risk factors and diseases[20, 25–27]. We evaluated the intra-class RORs of the ETN-treatment subset as well as the ADA-treatment subset.

Because the FAERS database does not contain information on the severity of ISR, this information was not taken into account in our analysis.

**Table 2. 2×2 contingency table.**

| Drug of interest | Adverse event of interest | All other adverse events of interest | Total |
|-----------------|--------------------------|-----------------------------------|-------|
| a                | b                         | c + d                             | a + b + c + d |
| All other drugs of interest | c                         | d                                 | c + d |
| Total            | a + c                     | b + d                             | a + b + c + d |

ROR\(^\text{a}\) = \frac{a \cdot d}{b \cdot c}.

95% CI\(^\text{b}\) = \sqrt{\frac{\text{ROR}}{a+b+c+d}}\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}\right).

\(^\text{a}\) Reporting Odds Ratio, \(^\text{b}\) Confidence Interval.
Results

The FAERS database contains 7,561,254 reports from January 2004 to December 2015. After excluding duplicate reports, 6,157,897 reports remained. Following selection for reports containing sex and age information, a final total of 3,839,264 reports were analyzed in this study. In total, 137,535 reports corresponded to case PTs (Tables 3, 4). The number of extracted reports of ISRs for GLM and CZM were low, and since INF is an IV-administered TNF-α inhibitor, we did not further investigate reports relating to these drugs. Other biological disease-modifying antirheumatic drugs (DMARDs), abatacept (T-cell action blocker) and tocilizumab (IL-6 inhibitor) were not included in our study.

For ETN, the crude RORs for ISRs stratified by age are summarized in Table 3. The < 20, 20−29, 30−39, 40−49, 50−59, 60−69, and ≥ 70-year-old groups contained 6,960, 9,384, 20,665, 37,823, 64,097, 51,481, and 25,737 reports relating to all adverse events, respectively. The < 20, 20−29, 30−39, 40−49, 50−59, 60−69, and ≥ 70-year-old groups contained 2,300, 3,219, 6,897, 11,314, 17,610, 11,587, and 4,501 reports relating to ISRs, respectively. The crude RORs (95% CIs) were 13.49 (12.83−14.19), 14.37 (13.76−15.00), 14.14 (13.73−14.56), 12.43 (12.15−12.71), 11.55 (11.34−11.76), 8.44 (8.27−8.63), and 5.86 (5.68−6.06), respectively. The adjusted RORs (95% CIs) for interaction terms for ETN* < 20, ETN* 20−29, ETN* 30−39, ETN* 40−49, ETN* 50−59, ETN* 60−69, and ETN* ≥ 70-year-old groups were 19.95 (18.86−21.11), 20.48 (19.48−21.52), 19.85 (19.10−20.63), 16.88 (16.32−17.45), 14.78 (14.34−15.24), 11.28 (10.92−11.66), and 8.09 (7.77−8.43), respectively (Table 3). All interaction terms were statistically significant (p < 0.0001) (Table 3). The crude RORs for ISRs in groups stratified based on therapy type are summarized in Table 3. The adjusted RORs (95% CIs) for ETN monotherapy, MTX monotherapy, and ETN + MTX combination therapy were 20.48 (19.48−21.52), 3.70 (3.60−3.80), and 18.30 (17.29−19.36), respectively.

Table 3. Crude and Adjusted ROR of etanercept for injection site reaction.

| Age (y.o.) | Total | Case | Crude ROR(95% CI) | Adjusted ROR(95% CI) | Likelihood ratio test |
|------------|-------|------|-------------------|----------------------|----------------------|
| <20        | 234,685 | 5,433 | 0.62 (0.61−0.64)  | 0.58 (0.55−0.60)     | <0.0001              |
| 20−29      | 265,823 | 9,716 | 1.02 (1.00−1.04)  | 1.02 (1.02−1.02)     | <0.0001              |
| 30−39      | 367,427 | 16,538| 1.31 (1.28−1.33)  | 1.11 (1.07−1.14)     | <0.0001              |
| 40−49      | 534,967 | 25,776| 1.45 (1.43−1.47)  | 1.18 (1.15−1.22)     | <0.0001              |
| 50−59      | 773,826 | 37,337| 1.50 (1.48−1.52)  | 1.13 (1.10−1.16)     | <0.0001              |
| 60−69      | 775,032 | 27,157| 0.97 (0.96−0.98)  | 0.89 (0.86−0.91)     | <0.0001              |
| ≥70        | 887,504 | 15,578| 0.41 (0.41−0.42)  | 0.54 (0.52−0.55)     | <0.0001              |

**ETN**
| ETN<20 | 216,147 | 57,428 | 16.00 (15.81−16.19) | 20.48 (19.48−21.52) | <0.0001 |
| MTX | 102,712 | 12,569 | 4.03 (3.95−4.11)  | 3.70 (3.60−3.80)     | <0.0001 |
| ETN+MTX | 27,451 | 6,759  | 9.19 (8.94−9.46)  | 18.30 (17.29−19.36) | <0.0001 |

**ETN** Age
| ETN<20 | 6,960 | 2,300 | 13.49 (12.83−14.19) | 19.95 (18.86−21.11) | <0.0001 |
| ETN<20−29 | 9,384 | 3,219 | 14.37 (13.76−15.00) | 20.48 (19.48−21.52) | <0.0001 |
| ETN<30−59 | 20,665 | 6,897 | 14.14 (13.73−14.56) | 19.85 (19.10−20.63) | <0.0001 |
| ETN<40−49 | 37,823 | 11,314 | 12.43 (12.15−12.71) | 16.88 (16.32−17.45) | <0.0001 |
| ETN<50−59 | 64,097 | 17,610 | 11.55 (11.34−11.76) | 14.78 (14.34−15.24) | <0.0001 |
| ETN<60−69 | 51,481 | 11,587 | 8.44 (8.27−8.63)  | 11.28 (10.92−11.66) | <0.0001 |
| ETN<70 | 25,737 | 4,501 | 5.86 (5.68−6.06)  | 8.09 (7.77−8.43)     | <0.0001 |

Table 4. Crude and Adjusted ROR of adalimumab for injection site reaction.

| Age (y.o.) | Total | Case | Crude ROR(95% CI) | Adjusted ROR(95% CI) | Likelihood ratio test |
|------------|-------|------|-------------------|----------------------|----------------------|
| <20        | 234,685 | 5,433 | 0.62 (0.61−0.64)  | 0.81 (0.78−0.85)     | <0.0001              |

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For ADA, the crude RORs for ISRs stratified by age are summarized in Table 4. For age-stratified groups, the < 20, 20–29, 30–39, 40–49, 50–59, 60–69, and ≥ 70-year-old groups contained 6,204, 15,007, 20,422, 28,644, 38,915, 29,453, and 16,059 reports relating to all adverse events, respectively. The < 20, 20–29, 30–39, 40–49, 50–59, 60–69, and ≥ 70-year-old groups were 1,582, 4,032, 6,405, 6,405, 7,962, 5,178, and 2,160 reports relating to ISRs, respectively. Crude RORs (95% CIs) for each of the same groups were 9.31 (8.79–9.86), 10.16 (9.79–10.53), 8.78 (8.50–9.07), 8.08 (7.86–8.31), 7.29 (7.11–7.47), 5.93 (5.75–6.11), and 4.23 (4.04–4.43), respectively. The adjusted RORs (95% CIs) for interaction terms for ADA* < 20, ADA* 20–29, ADA* 30–39, ADA* 40–49, ADA* 50–59, ADA* 60–69, and ADA* ≥ 70-year-old groups were 16.07 (15.08–17.13), 16.18 (15.46–16.92), 13.91 (13.34–14.51), 12.77 (12.29–13.28), 11.30 (10.89–11.73), 9.39 (9.02–9.79), and 6.90 (6.54–7.27), respectively (Table 4). All interaction terms were statistically significant (p < 0.0001) (Table 4). The crude RORs for ISRs in groups stratified based on therapy type are summarized in Table 4. The adjusted RORs (95% CIs) for ADA monotherapy, MTX monotherapy, and ADA + MTX combination therapy were 16.18 (15.46–16.92), 3.59 (3.50–3.68), and 15.05 (14.24–15.91), respectively.

### Discussion

RA is an autoimmune disease and a chronic inflammatory disorder. Despite novel therapies such as TNF-α inhibitors entering the market, RA treatment strategy has generally comprised of case control, pain mitigation, and increasing QoL for patients[7, 8]. This is largely because ISR has been found to be a relatively common side effect of injectable TNF-α inhibitors[28–31]. ISR usually occurs within the first month of treatment, lasting for 3 to 5 days[32]. Although most cases of ISR resolve themselves, symptomatic eruptions are treated with corticosteroids, antihistamines, acetaminophen, or cold compresses[32]. The effect of ISR on clinical outcomes for RA is unknown, but research involving multiple sclerosis patients that shows pain during and after injections has been found to affect adherence to drug regimen[33]. Side effects such as ISR may similarly be an important factor involved in the patient preference for SC TNF-α inhibitors and treatment adherence.

Our results suggest that ETN and ADA monotherapy does induce ISRs, while MTX combination therapy with ETN or ADA decreases the incidence of this adverse event. Our findings also suggest that aging may influence the adjusted RORs for ETN or ADA therapy based on the logistic regression analysis performed using the FAERS database.

ISR commonly occurs in biologic DMARDs such as TNF-α inhibitors administered via SC injections, and is becoming more clinically important as the number of biologic therapies available for RA therapy increases. ETN and ADA were both found to be associated with ISR in the FAERS database. The adjusted RORs for ADA treatment were lower than those for ETN treatment. ETN was administered to RA patients once or twice per week[1, 2]. On the other hand, ADA was administered once every two weeks[3]. The difference in administration frequency between ETN and ADA may be the cause for the high crude and adjusted RORs for ETN therapy when compared to RORs for ADA therapy (Tables 3, 4). Perhaps since GLM is a biologic agent which is administered once a month[4], the number of reports regarding adverse events induced by GLM was found to be low. Multiple studies of drug adherence across a
variety of medications have reported an inverse relationship between dosing frequency and drug adherence[34–36], and patients have been found to prefer longer dosing intervals when given the option[37–39]. Another plausible reason for the differences in RORs is the varying composition of different TNF-α inhibitors, which can range from a complex composition with strong buffering capacity[3] to a more simple composition with weak buffering capacity[5]. Further work to better understand potential mechanisms of ISR and the consequent clinical implications is needed.

Analysis using a logistic model allows for adjustment of confounding factors included in crude ROR calculation. The 95% CIs lower limits for crude and adjusted RORs for both ETN and ADA therapy were above 1 (Tables 3, 4, Fig 1). Adjusted RORs for ETN* ≥ 70 and ADA* ≥ 70 were the lowest in each age-stratified group (Tables 3, 4, Fig 1). Therefore, in our study, we have demonstrated that adjusted RORs decreased with an increase in age.

Figure 1. Adjusted reporting odds ratios and 95% confidence intervals. Open circles and triangles: adjusted reporting odds ratios and 95% confidence intervals for age analyzed by TNF-α inhibitor drug, etanercept and adalimumab, respectively. Filled circles and triangles: adjusted reporting odds ratios and 95% confidence intervals for etanercept- and adalimumab-associated injection site reaction, respectively.

Regarding effectiveness, several clinical studies have suggested that treatment of RA with TNF-α inhibitor drugs should be in combination with MTX[42–46]. The guidelines also suggest that ETN + MTX combination therapy is more effective than ETN monotherapy[7, 8]. From the perspective of safety, the reporting ratio of other severe adverse events, such as infection, for ETN + MTX combination therapy is similar to that for ETN monotherapy[42–46]. The adjusted RORs of ISRs for ETN + MTX combination therapy and ADA + MTX combination therapy were lower than those for their respective monotherapies (Tables 3, 4). Therefore, our result strengthens the credibility of ETN + MTX combination therapy in the clinical setting.

We do not have a conclusive explanation for these data. To the best of our knowledge, systematic studies of ISR that are stratified by age group are rare. Additionally, the biological mechanisms that mediate ISR by SC TNF-α inhibitors are not well understood. Therefore, ISR may be related to inflammatory mediators that are released during non-immune-stimulated mast cell degranulation[40]. Immune function decreases with age owing to the reduced function of T lymphocytes[41]. A plausible reason for our result may therefore be related to the differences in sensitivity to medication between younger and older patients.

Immune function decreases with age owing to the reduced function of T lymphocytes[41]. A plausible reason for our result may therefore be related to the differences in sensitivity to medication between younger and older patients.

Because of these limitations, crude RORs without logistic regression analysis do not indicate the risk of adverse event occurrence in absolute terms, and can only offer a rough indication of signal strength[15]. For this reason, we partially refined the results with a dedicated correction in order to detect possible confounders present in the database using logistic regression and subset analysis. Consequently, we believe that despite the limitations, it may be acceptable to compare the adjusted RORs of a
particular adverse event derived from stratified analysis within a particular context. However, further research is needed in order to more accurately determine the specific associations between TNF-α inhibitors and ISR.

When discussing SC TNF-α inhibitor treatment for RA, ISR may be an important factor for patient comfort and safety as well as therapeutic efficacy. Our results show that younger patients should be closely monitored for ISR when they are administered a SC TNF-α inhibitor. It is important to provide patients with information regarding the tolerability of SC TNF-α inhibitors. We hope that our research may make a valuable contribution to the information available to clinicians in order to improve the management of RA and to allow patients to make a more informed treatment choice.

Conclusions

This study was the first to evaluate the correlation between aging and induction of ISRs by TNF-α inhibitors using SRS analysis strategy. We demonstrated that overall, the adjusted RORs in younger patients were comparatively high. Therefore, we can infer that younger RA patients receiving ETN or ADA treatment should be closely monitored for ISR symptoms. We also provided evidence of higher efficacy of combined therapy comprising ETN and MTX administration. Our results may potentially be used in clinical practice to improve the management of RA and ISRs adverse events.

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Competing Interests

JA is an employee of Medical Database. The rest of the authors have no conflict of interest.

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