Effectiveness of biologic and non-biologic antirheumatic drugs on anaemia markers in 153,788 patients with rheumatoid arthritis: New evidence from real-world data

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A R T I C L E  I N F O

Keywords: Tocilizumab IL-6 receptor inhibitor Change in anaemia markers Real-world data Comparison of biologic and non-biologic DMARDs

Background: To evaluate the impact of treatment with disease-modifying antirheumatic drugs (DMARDs), including IL-6 receptor inhibitor tocilizumab (TCZ), on anaemia markers in patients with rheumatoid arthritis.

Methods: Using the Centricity Electronic Medical Records from USA, patients with rheumatoid arthritis diagnosed between January 2000 and April 2016, who initiated TCZ (n = 3732); tofacitinib (TOFA, n = 3126); other biologic DMARD (obDMARD, n = 55,964); or other non-biologic DMARD (nbDMARD, n = 91,236) were identified. Changes in haemoglobin (Hb) and haematocrit (Hct) over 2 years of treatment initiation were evaluated, adjusting and balancing for confounders.

Results: Mean (95% CI) adjusted increase in Hb and Hct levels at 24 months in TCZ group were 0.23 g/dL (0.14, 0.42) and 0.96% (0.41, 1.52) respectively. Among patients with anaemia in the TCZ group, Hb and Hct increased significantly by 0.72 g/dL and 2.06%, respectively. Patients in the TCZ group were 86% (95% CI of OR: 1.43, 2.00) more likely to increase Hb ≥ 1 g/dL compared to the other groups combined. No clinically significant changes in Hb were observed in the other groups. The obDMARD group demonstrated lower Hct increase than TCZ group, while no significant changes were observed in the remaining groups. Compared to those who initiated TCZ therapy after 1 year of diagnosis of rheumatoid arthritis, those who initiated earlier were 95% (OR = 1.95; 95% CI: 1.19, 3.21; p < 0.001) more likely to increase Hb within 6 months.

Conclusions: This real-world study suggests significant increase in Hb and Hct levels after TCZ therapy in anaemic and non-anaemic patients with rheumatoid arthritis, compared with other biologic and non-biologic DMARDs.

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Background

Rheumatoid arthritis (RA) is a chronic, inflammatory, autoimmune disease of unknown aetiology, affecting up to 1.3% of people worldwide [1,2]. In the last decade, there have been significant advances in the treatments for RA, especially for patients who are not responding to traditional disease-modifying antirheumatic drugs (DMARDs). A number of clinical studies have reported significant efficacy of biologic DMARDs in terms of reducing RA symptoms, slowing the rate of disease progression, and improving physical function and quality-of-life measures in patients with moderate to severe RA [3–5].

Anaemia is often present in people with active RA, and is typically characterised by low serum iron concentrations in
conjunction with normal or increased iron storage [6]. It has been associated with physical disability and increased mortality in patients with RA [7,8]. Recent studies suggest that anaemia in chronic disease develops via multiple mechanisms including pathogenic iron homeostasis, impaired erythropoiesis, and the blunted erythropoietin response [9,10]. Inflammatory cytokines such as IL-6 and TNF-α are critically involved in this process. For example, IL-6 induces hepcidin, a critical regulator of iron metabolism in anaemia [10,11], while TNFα and IL-1 impair erythropoiesis and induce the blunted erythropoietin response. Among various mechanisms, studies suggest the central role of hepcidin and IL-6 for the pathophysiology of anaemia [10,11].

Given the central role of IL-6 in anaemia of chronic disease, it is possible that tocilizumab (TCZ) therapy could improve anaemia markers more effectively than other biologics [10]. However, population-level studies evaluating the possible association of treatment with various biologic and non-biologic DMARDS are lacking. Hashimoto et al. [12] evaluated the change in haemoglobin (Hb) levels at 12 weeks in 147 patients treated with TCZ compared with patients treated with other biologic DMARDS (obDMARDS). Song et al. [13] evaluated the effects of treatment with TCZ and TNF-α in 93 patients with RA over 16 weeks, and concluded that TCZ was more effective than TNF-α inhibitors for improving anaemia. We are not aware of any observational study that evaluated the possible association of various antirheumatic therapies in a holistic way in the real-world setting. Also, studies evaluating the possible benefits of early initiation of biologic DMARDS on anaemia factors is scarce. The aetiology of anaemia in RA is multifactorial and anaemia of chronic disease is not the only cause of anaemia in RA. The Hb levels after treatment may be influenced by various factors such as baseline characteristics, concomitant treatment, or clinical response to treatment. Hence such evaluations must be conducted on a reasonably larger number of patients with appropriate follow-up data.

Using large primary/ambulatory care patient-level data with reasonable follow-up, the aims of this study of patients with RA were to evaluate (1) change in Hb and haematocrit (Hct) over 6, 12, and 24 months of commencing treatment with TCZ, tocilizumab citrate (TOFA); obDMARDS, and other non-biologic DMARDS (nbDMARDS), and (2) if early initiation of treatment with TCZ is beneficial in the management of anaemia factors, compared to other therapies.

Methods

Data source

In the USA, the Centricity Electronic Medical Record (CEMR) database represents a variety of ambulatory and primary care medical practices, including solo practitioners, community clinics, academic medical centres, and large integrated delivery networks. Over 35,000 physicians and other providers from all US states contribute to the CEMR, of which approximately 75% are primary care providers. The database is generally representative of the USA population, and has been extensively used for academic research worldwide [14–17].

For more than 34 million individuals, longitudinal electronic medical records were available from 1995 till April 2016, with the condition of availability of live records (including “Home Care Report” and “Registration Update”) on or after January 1, 2014. This database contains comprehensive patient-level information on demographics, anthropometric, clinical and laboratory variables including age, sex, ethnicity, smoking status, and longitudinal measures of body weight, body mass index (BMI), blood pressure, Hct, Hb, urine albumin and creatinine, and serum creatinine.

All disease events (RA, anaemia, comorbidities, etc.) along with dates are coded with ICD-9, ICD-10, or SNOMED CT codes. Medication data includes brand names and doses for individual medications prescribed (RxNorm), start/stop dates and specific fields to track treatment alterations. This dataset also contains patient-reported medications, including prescriptions received outside of the CEMR network and over-the-counter medications.

Participants

Following identification of patients with RA, the following inclusion criteria were applied: (1) age at diagnosis ≥18 and ≤80 years, (2) diagnosis date on or after 1 January 2000 to 30 April 2016, (3) no missing data on age, sex, and ethnicity, (4) complete data on Hb and Hct at index date, and (5) initiated a DMARD at the time of diagnosis or during the follow-up period.

Variable definitions

The original medication names from the EMR source systems were text-mined for the defined generic names and corresponding brand names approved by FDA (including drug combinations). The following non-biologic disease-modifying antirheumatic drugs (nbDMARDS) were identified: methotrexate (MTX), sulfasalazine, leflunomide, hydroxychloroquine, chloroquine, minocycline, TOFA, azathioprine, cyclophosphamide, penicillamine, cyclosporine, aurenofin, and mycophenolate (mofetil or sodium). The biologic disease-modifying antirheumatic drugs (bDMARDS) included: abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, and TCZ. All generic names listed under ‘M01A’ class of Anatomical Therapeutic Chemical (ATC) Classification System and acetylsalicylic acid (Aspirin, ATC code ‘B01AC06’) were considered as non-steroidal anti-inflammatory drugs (NSAIDs). ATC codes of ‘H02’ and ‘N02A’ classes were used to obtain generic names for corticosteroids and opioids, respectively.

In the study cohort the following treatment groups were defined:

1. TCZ: those who were prescribed TCZ, and never received TOFA;
2. TOFA: those prescribed TOFA, and never received TCZ;
3. obDMARD: those prescribed bDMARD, and never received TCZ or TOFA;
4. nbDMARD: those prescribed nbDMARD, and never received any bDMARD or TOFA.

Index date was defined accordingly to first prescription of the drugs within each of the four groups, on or post diagnosis of RA.

Demographic variables included gender, age, and ethnicity. Measures of body weight, body mass index (BMI), and systolic blood pressure were calculated as the average of available measurements within a 3-month window of the index date. Obesity was defined as BMI ≥ 3 kg/m². Longitudinal measurements of Hb and Hct were arranged on the basis of non-overlapping 6-monthly windows, which were defined progressively from the time of index date. In the study cohort at least 50% of patients had two or more longitudinal follow-up measures on Hb and Hct post index dates during the 24 months of follow-up.

The missing data post index date were imputed using multiple imputation technique based on the Markov Chain Monte Carlo (MCMC) method with adjustments for age, sex, appropriate concomitant medications, and duration of RA [18].

The presence of comorbidities prior to the index date was also obtained. Cardiovascular disease (CVD), cancer, chronic kidney disease (CKD), and diabetes (type 1 and type 2) were identified by relevant disease classification codes. Cardiovascular disease was...
defined as ischaemic heart disease (including myocardial infarction), peripheral vascular arterial disease, heart failure, or stroke. Cancer was defined as any malignant neoplasm or carcinoma in situ. Anaemia was defined as the presence of a clinical diagnosis of anaemia (ICD-9, ICD-10, and SNOMED CT codes) or on the basis of Hb < 12/13.5 g/dL for female/male at index date.

**Statistical methods**

Baseline characteristics at time of index date were summarised as number (%), mean, and standard deviation (sd) for normally distributed data, and median and interquartile range (IQR) for data with skewed distribution.

Given the observational nature of this study, and significant differences in risk factors between the comparator treatment groups, we used the “Treatment Effect” modelling approach that helps to draw robust inferences through appropriate adjustments and balancing of confounders [19–22]. The inverse-probability-weighted regression adjustments were applied while evaluating the changes in Hb and Hct during follow-up from index date. In patients with minimum DMARD exposure of 6, 12, or 24 months, changes in Hb and Hct were calculated at 6, 12, and 24 months, respectively. Adjustments were made for age, sex, and duration of RA history of CVD, CKD, cancer, and diabetes prior to index date.

The treatment groups were balanced on sex, number of concomitant medications, duration of RA and baseline measures for both analyses. The potential outcome means and robust 95% confidence interval (CI) of changes were estimated. Separate analyses were conducted in patients with anaemia at index date.

As C-reactive protein (CRP) at index date may influence the observed effectiveness of individual drugs on Hb level, a separate adjusted analysis was conducted by adjusting for the baseline CRP. Sensitivity analyses included separate analysis by sex, and for complete available data.

To evaluate the likelihood of increasing Hb level ≥1 g/dL, and to explore possible benefit of early initiation of bDMARDs (within 1 year of RA diagnosis) in terms of increasing the Hb levels during follow-up, multivariable logistic regression models were fitted with adjustments for the confounders as described above. The adjusted odds ratio and 95% CI were reported.

**Results**

Of the 283,756 patients diagnosed with RA in the CEMR database, 272,621 had diagnosis on or after 1 January 2000 (Fig. 1). Employing the inclusion criteria, the study cohort consisted of 153,788 patients. The study cohort were 77% female, of mean (SD) 58 years old, 71% White Caucasian, 22% were current or ex-smokers, and 43% were obese at index date (Table 1). The proportion of female patients in the TCZ and TOFA groups were the same (82%), while the other two DMARD groups had significantly lower proportions of females (76%). With similar age distribution among the treatment groups, the time to initiation of therapy from diagnosis (duration of RA) was similar in the TCZ and TOFA groups (39 months). The average duration of RA in the obDMARD/obnDMARD groups were significantly lower (12/4 months). The proportions of patients with anaemia at index date in the TCZ, TOFA, obDMARD, and obnDMARD were 26%, 29%, 21%, and 24% respectively.

In the cohort with 3.5 years of mean follow-up from index date, patients in the TCZ/TOFA groups had significantly lower follow-up time (2.0/1.2 years). The proportions of patients with minimum 1/2 years of follow-up in the TCZ and TOFA groups were 53/42% and 67/20% respectively, while overall 58% of the cohort had a minimum 2 years of follow-up.

The prescription patterns for different anti-rheumatoid drugs prior and post index date in the TCZ and TOFA groups are described in Supplementary Table 1. Proportions of patients who received MTX prior to the initiation of TCZ/TOFA were 58/49% respectively, while 56/39% added MTX post index date. During mean 2 years of follow-up time in the TCZ group, 55% moved to other bDMARDs. In the TOFA group, 30% patients added or moved to bDMARDs within a mean of 1.2 years follow-up.

The number of patients with minimum 6/12/24 months of treatment duration in the TCZ, TOFA, obDMARD, and obnDMARD were 2,636/1,817/896; 1,828/1,080/327; 45,567/38,845/28,827, and 71,678/60,202/43,234 respectively. The mean (95% CI) adjusted trajectories of Hb and Hct over 30 months from 6 months prior to the index date are presented in Figure 2 (A and C) by the treatment groups, for those who had a minimum 1 year of respective treatment post index date (n = 101,944). Separate trajectories for patients with anaemia at index date are presented in Figure 2 (B and D). The trajectories of anaemia factors over 30 months for all patients irrespective of treatment duration (intention-to-treat) are presented in Supplementary Figure 1.

Patients treated with TCZ showed significant increases in both anaemia parameters within 6 months of treatment compared to other groups. The mean (95% CI) adjusted increase in Hb level at 6- and 24-month follow-up in TCZ group were 0.22 (0.14, 0.30) g/dL and 0.23 (0.14, 0.42) g/dL, respectively (Table 2). Among patients with anaemia at index date, the adjusted mean (95% CI) increase in Hb level were 0.40 (0.24, 0.56) g/dL and 0.72 (0.36, 1.08) g/dL respectively. The observed increase in Hb levels among patients in the obDMARD group were significantly lower compared that achieved by patients treated with TCZ. Among patients with anaemia at index date, those treated with TCZ were 86% (OR = 1.86; 95% CI: 1.43, 2.00; p < 0.001) more likely to increase Hb ≥ 1 g/dL at 2 years, compared to other treatment groups. Compared to those in the TOFA group, anaemic patients in the TCZ group were 67% (OR = 1.67; 95% CI: 1.54, 1.98) more likely to increase Hb ≥ 1 g/dL at 2 years. No clinically significant change in Hb level was observed in the other treatment groups during 2 years of follow-up (Table 2). However, all patients with anaemia at index date increased their Hb levels statistically significantly in the non-TCZ groups also.

The mean adjusted increase in Hct level at 6- and 24-month follow-up in TCZ group were 0.78% (95% CI: 0.28, 1.28) and 0.96% (95% CI: 0.41, 1.52), respectively (Table 3). Among patients with anaemia at index date, the adjusted mean (95% CI) increase in Hct...
level were 1.08 (0.56, 1.60)% and 2.06 (1.06, 3.06)%, respectively. Among all patients, the observed increase in Hct levels among patients treated with obDMARD were significantly lower compared that achieved by patients treated with TCZ. No clinically significant change in Hct level was observed in the other treatment groups during 2 years of follow-up.

Separate analyses with adjustments for CRP at index date revealed similar Hb control in the TCZ group. Sensitivity analyses by gender and with complete cases showed similar results.

In the TCZ group, those who initiated the therapy within 1 year of RA diagnosis, were 95% (OR = 1.95; 95% CI: 1.19, 3.21) more likely to achieve the Hb level significantly at 6 months of treatment. However, early initiation of treatment with obDMARD (OR = 0.98, p = 0.76), onbDMARD (OR = 1.19, p = 0.055) or TOFA (OR = 1.19, p = 0.55) were not associated with the increased likelihood of achieving better Hb levels. Among all patients initiating respective therapies within one year of RA diagnosis, compared to the TOFA group, only those treated with TCZ had 2.8 (95% CI of OR: 1.70, 4.67) times significantly higher likelihood of achieving better Hb control at 6 months.

### Discussion

In this longitudinal cohort study in a large number of patients treated with different biologic and non-biologic anti-rheumatoid therapies with mean 3.5 years of follow-up data, we have shown that (1) RA patients treated with TCZ significantly increase the Hb and Hct level over 2 years of treatment irrespective of their baseline anaemia status, (2) treatment with other biologic DMARDs were not associated with any clinically meaningful benefits on anaemia markers, (3) no benefits of treatment with TOFA on Hb and Hct, (4) anaemic patients treated with TCZ are significantly more likely to increase Hb ≥ 1 g/dL compared to other biologic and non-biologic therapies, while the levels of both Hb and Hct significantly increased during 24 months of treatment in all treatment groups among patients with anaemia at therapy initiation, and (5) earlier initiation of treatment with TCZ was associated with significantly higher likelihood of achieving better Hb level during follow-up, while earlier therapy initiation with other biologic DMARDs or TOFA were unlikely to be associated with early benefits with Hb.

Clinical practice guideline on anaemia management suggests an Hb increase by 1 g/dL in an average size adult with anaemia. We have observed a significant increase in Hb level in the population at 6 and 24 months post initiation of TCZ in anaemic patients, with 86% higher likelihood of increasing Hb level above 1 g/dL compared to other biologic and non-biologic therapies. In the registry study in Japanese people, Mori et al. [23] reported average increase of Hb over 6 months by 0.96 g/dL and 0.89 g/dL in TCZ-treated anaemic patients with and without renal insufficiency (n = 72). The observed higher increase in Hb in the Japanese registry study is likely due to modelling approach to adjust for confounders.

Given the observed benefits of treatment with TCZ, one of the novelties of this study is the evaluation of the possible benefits of early initiation of IL-6 based therapies (post diagnosis of RA) for more efficient short- and long-term control of anaemia markers. Our robust analyses based on reasonably large number of patients suggest almost 2-fold higher likelihood of achieving increased Hb levels within 6 months of therapy among those who initiated TCZ within 1 year of the diagnosis of RA, compared to those who initiated later. While a systematic review of studies have evaluated the possible benefits of treatment with TCZ at early stage of RA development in
Fig. 2. For those with minimum 1 year of treatment duration within each group: (A) unadjusted longitudinal changes (95% CI) in haemoglobin by treatment groups; (B) in those with anaemia at index date, unadjusted longitudinal changes (95% CI) in haemoglobin by treatment groups; (C) unadjusted longitudinal changes (95% CI) in haematocrit by treatment groups; (D) in those with anaemia at index date, unadjusted longitudinal changes (95% CI) in haematocrit by treatment groups.

Table 2
Change in haemoglobin at 6, 12, and 24 months from index date. Treatment groups balanced on sex and baseline measures. Analysis was adjusted for age, sex, and duration of RA, history of CVD, CKD, cancer, and diabetes prior to index date

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean (95% CI) g/dL at index date</th>
<th>Changes at 6 months (g/dL) mean (95% CI)</th>
<th>Changes at 12 months (g/dL) mean (95% CI)</th>
<th>Changes at 24 months (g/dL) mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCZ</td>
<td>13.26 (13.12, 13.3)</td>
<td>0.22 (0.14, 0.3)</td>
<td>0.24 (0.13, 0.36)</td>
<td>0.23 (0.14, 0.42)</td>
</tr>
<tr>
<td>TOFA</td>
<td>13.04 (12.99, 13.09)</td>
<td>0.06 (0.04, 0.07)</td>
<td>0.06 (0.04, 0.09)</td>
<td>0.04 (0.02, 0.07)</td>
</tr>
<tr>
<td>obDMARD</td>
<td>13.27 (13.26, 13.29)</td>
<td>-0.06 (−0.10, -0.02)</td>
<td>-0.05 (−0.09, −0.02)</td>
<td>-0.08 (−0.1, −0.06)</td>
</tr>
<tr>
<td>onbDMARD</td>
<td>13.14 (13.14, 13.15)</td>
<td>-0.03 (−0.06, 0.01)</td>
<td>-0.04 (−0.09, 0.03)</td>
<td>-0.03 (−0.09, 0.02)</td>
</tr>
</tbody>
</table>

Table 3
Change in haematocrit at 6, 12, and 24 months from index date. Treatment groups balanced on sex and baseline measures. Analysis was adjusted for age, sex, and duration of RA, history of CVD, CKD, cancer, and diabetes prior to index date

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean (95% CI) % at index date</th>
<th>Change at 6 months (%) mean (95% CI)</th>
<th>Change at 12 months (%) mean (95% CI)</th>
<th>Change at 24 months (%) mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCZ</td>
<td>39.86 (39.74, 39.98)</td>
<td>0.78 (0.28, 1.28)</td>
<td>1.08 (0.56, 1.6)</td>
<td>1.48 (0.86, 2.1)</td>
</tr>
<tr>
<td>TOFA</td>
<td>39.53 (39.41, 39.66)</td>
<td>-0.03 (-0.34, 0.29)</td>
<td>1.00 (0.48, 1.52)</td>
<td>1.43 (0.81, 2.06)</td>
</tr>
<tr>
<td>obDMARD</td>
<td>39.73 (39.7, 39.76)</td>
<td>0.14 (0.01, 0.28)</td>
<td>0.50 (0.4, 0.6)</td>
<td>0.89 (0.73, 1.05)</td>
</tr>
<tr>
<td>onbDMARD</td>
<td>39.43 (39.4, 39.45)</td>
<td>-0.03 (-0.06, 0.01)</td>
<td>0.41 (0.34, 0.48)</td>
<td>0.74 (0.63, 0.86)</td>
</tr>
</tbody>
</table>
terms of disease remission, no study, to the best of our knowledge, have evaluated the comparative possible benefits of early initiation of biologic and non-biologic therapies on anaemia markers [24].

Generally primary care databases contain information on medication prescriptions provided to the individual in the form of prescription date and number of refills, and less frequently capture dispensed prescription data. The main strength of this study is availability of the data from patients’ medication lists that included prescribed medications within the EMR network and also medication information that could be prescribed outside of the EMR. The CEMR database also tracks longitudinal treatment adjustments. Furthermore, we have used robust algorithms to aggregate medication data at patient level. Finally, the database contains comprehensive clinical information, which is usually not available in claims databases.

The limitations of this study include non-availability of complete and/or reliable data on: (1) medication adherence and side-effects; (2) disease activity and pain scores; (3) longitudinal data on doses of individual therapies; (4) socioeconomic status; and (5) insurance type. We could not evaluate the possible synergy between increased levels of anaemia factors and benefits in terms of RA disease state because of the non-availability of adequate data on disease activity scores. The database extract used in this study included all patients with any chart-related activity on or after 2014, which could lead to a potential selection bias. However, this is likely to represent contemporary practice in patients with RA who are receiving ongoing therapies. For the same reasons, we have included only those patients with a RA diagnosis on or after January 2000. Missing risk factor data in longitudinal observational studies is a common problem, and studies have evaluated the applicability of sophisticated imputation techniques for missing longitudinal data in EMRs, including this CEMR database [17,18,25]. In the absence of robust data on quality of life (QoL) in the CRMR database, we could not evaluate the possible association of change in Hb with QoL, limiting our ability to infer upon the potential clinical impact of increase in Hb and Hct on the overall wellbeing of the patients.

Conclusions

In conclusion, this study has shown that in patients with RA, treatment with TCZ was associated with significant improvement in anaemia markers after adjusting for confounding factors, whereas other biologic DMARDs or TOFA were significantly less effective in improving anaemia markers. However, future population-level clinical research is needed to determine whether the observed improvement in anaemia markers in TCZ-treated patients is associated with meaningful improvements in relevant aspects of quality of life such as fatigue, and in better disease control, the aspects where robust data are very limited.

Declarations

Ethics approval and consent to participate

This study was exempt from ethics approval from an institutional review board and informed consent because, according to the US Department of Health and Human Services Exemption 4 (CFR 46.101(b) (4)), the research involved the study of existing data, and the subjects could not be identified directly or through identifiers linked to the subjects.

Availability of data and material

The analysed database is not publicly available due to licence agreement, but aggregated datasets may be requested from the corresponding author.

Acknowledgements

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Competing interests

S.K.P. has acted as a consultant and/or speaker for Novartis, Gl Dynamics, Roche, AstraZeneca, Guangzhou Zhongyi Pharmaceutical and Amynin Pharmaceuticals LLC. He has received grants in support of investigator and investigator-initiated clinical studies from Merck, Novo Nordisk, AstraZeneca, Hospira, Amynin Pharmaceuticals, Sanofi-Avenis, Pfizer, and Roche. J.H.B., A.P.S., S.G., and K.S. are Roche Group employees. O.M. has no conflict of interest to declare.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.semarthrit.2017.08.001.

References


