A biopsychosocial model of pain and depression in rheumatoid arthritis: a 12-month longitudinal study

T. Covic, B. Adamson, D. Spencer and G. Howe

Objective. To cross-validate a biopsychosocial model using physical disability, helplessness and passive coping to predict depression and pain in rheumatoid arthritis (RA).

Methods. Clinical and psychological measures were collected from 157 RA patients at three time points over a period of 12 months. Path analysis was used for cross-sectional and longitudinal prediction of depression and pain.

Results. Helplessness and passive coping were found to be significant mediators of the relationship between the physical disability and future depression and pain. Cross-sectionally, the predictive model could account for 52–94% of the variance of pain and 37–71% of the variance of depression. Longitudinally, the predictive model could explain 29–43% of the variance of pain and 21–33% of the variance of depression.

Conclusions. These results suggest that physical disability, helplessness and passive coping have a significant impact on the levels of pain and depression experienced by RA patients.

Key words: Biopsychosocial model, Rheumatoid arthritis, Physical disability, Pain, Helplessness, Passive coping, Depression.
and OA subjects (n = 100) found physical disability and marital status to be the key predictors of clinical depression [9]. In contrast, a 4-yr longitudinal study of quality of life found fatigue and pain to be the most significant predictors of physical disability and psychosocial outcomes [10]. In a 3-yr longitudinal study of subjects with RA of longer duration, passive strategies, such as decreasing activity, were found to have a negative effect on future depression and disease impact (work, household and leisure activities) [11]. In a 5-yr longitudinal study of 182 RA subjects, psychological and physical outcomes remained stable over time and while physical function was predicted by psychological status and age, psychological status after 5 yr was predicted only by baseline psychological status [12].

The inconsistent results discussed above do not lend themselves to clinical application. The inconsistency may be due to a number of different factors, including methodological limitations such as cross-sectional [3, 5, 7] vs longitudinal [8, 11, 12] analyses, survey vs interview mode of data collection, and different assessment tools. Conceptual differences, such as using pain as an indicator of a process vs outcome of RA, also play a significant part in these results. Additionally, there is the unpredictable and chronic nature of RA, which may be reflected in the changing importance of key factors. For example, physical factors may dominate during the acute stages of disease (i.e. flare-ups) while psychological factors may have a greater impact over time (the perceived loss of quality of life due to the disease). Subsequently, there is considerable evidence for the correlation between the biopsychosocial factors, but the causal relationship remains unclear, as does the direction of the effects, which may be bidirectional [13]. For example, physical disability and pain may lead to depression, but the fact that the majority of RA patients do not experience depression suggests that factors other than RA may be influential [13]. Coping is certainly one factor that mediates the relationship between physical and psychological factors [6, 7, 11]. Perception of the significance of some functional losses, such as valued activities, is another important factor. A 4-yr longitudinal study found that decline in valued activities (such as leisure and social functions) was most closely related to new depression symptoms [14].

The present study used a model that integrates the key factors identified in previous studies. It was originally tested in a cross-sectional study [7] and found to account for 49% of the variance of pain and 50% of the variance of depression, considerably more than models proposed in other studies. It postulates that the disease activity affects both pain and depression and is mediated by passive coping and helplessness. Physical (functional) disability is treated as an indicator of disease activity and was measured with the Health Assessment Questionnaire (HAQ). Wolfe [15], in a large, longitudinal study, confirmed the sensitivity of the HAQ to change as a measure of disease effect, and found it closely related to pain, disease activity [erythrocyte sedimentation rate (ESR)] and psychological factors. Furthermore, physical disability may be treated as an indicator of both process and outcome, but more commonly of process [15]. In this model, both pain and depression are viewed as outcomes of RA, with the understanding that depression may also be caused by factors other than disease factors. Coping, which refers to the strategies applied in dealing with one’s disease, and helplessness, which refers to the cognitive appraisal of lack of control, mediate the impact of disease activity on pain and depression.

Thus, this model is suggesting that RA is experienced at both the physical (pain) and psychological (depression and pain) levels because its impact is filtered through the psychological factors of coping and helplessness. Even the physical indicator of disease activity (physical disability) is likely to have both physical and psychological elements [16], which serves only to illustrate further the biopsychosocial experience of the disease. This is conceptually a comprehensive model that addresses not only the clinical factors (physical disability, pain) but also perceptual (helplessness) and cognitive and behavioural activities (coping).

In order to test the robustness of this model empirically and to overcome some of the methodological and conceptual variations evident in previous research, the aim of this study was to test the hypothesized model both cross-sectionally and longitudinally over a period of 12 months. Ultimately the purpose is to provide a model that may have clinical value in the management of RA.

**Methods**

**Procedure**

Participants were recruited from three rheumatology practices. Informed consent was obtained from all participants and the study was approved by the institutional ethics committee. Convenience sampling was necessary to verify the RA diagnosis according to the 1987 American College of Rheumatology criteria [17] and the participants’ current status of RA management. The recruitment took place during the patients’ regular consultation. Three survey measures were collected from the participants at intervals of approximately 4 months (Times 1, 2 and 3).

**Participants**

There were 157 participants, of whom 76% were female and 24% male. The majority (73%) had attained 10 yr of schooling and 71% were not working (56% retired, 15% unemployed or house duties). The majority of participants were married (71%). Their age ranged from 29 to 80 yr, with a mean of 57.85 (s.d. = 12.24) yr. Most participants were born in Australia (75%), RA duration ranged from 6 months to 47 yr, with a mean of 13.07 (s.d. = 9.45) yr. The retention rate at second and third data collection (Times 2 and 3) was 85 and 83% respectively. In terms of the medication usage, 95.5% of participants used medication daily. The majority of patients (99%) used disease-modifying anti-rheumatic drugs. Most common of these were methotrexate (77%), followed by prednisone (56%) and sulphasalazine (40%). The majority (68%) were on more than one drug. Their medication remained predominantly unchanged over the 12-month
period (60–66%). When the medication needed adjustment, this commonly consisted of an increase in the dose of the current medication or addition of another medication (21–31%). This information was gathered as an indicator of RA stability or variability over time.

**Measuring instruments**

The following measures were obtained for all participants in the study.

**Dependent variables.** Pain was measured with the five-item subscale of the Arthritis Impact Measurement Scales (AIMS) [18]. Scores range from 1 to 10, a higher score indicating greater pain. Depression was measured with the 20-item Center for Epidemiologic Studies—Depression Scale [19]. Scores above 16 are considered high.

**Independent variables.** Physical disability was measured with the eight-item Modified Health Assessment Questionnaire (MHAQ) [20]. RA duration was recorded in years. Helplessness was measured with the five-item subscale of the Arthritis Helplessness Index [21], which is designed to assess the perception of loss of control. Coping was measured with 44-item Pain Coping Strategies Questionnaire [22]. This consists of seven subscales and two effectiveness items. Scores range from 0 to 36 for each subscale. Subscales can also be grouped into Passive and Active coping subscales [23]. The Passive coping subscale consists of two subscales totalling 12 items: Catastrophizing (CAT) and Praying and Hoping (PH), with scores ranging from 0 to 72. The Active Coping subscale consists of five scales totalling 30 items: Coping Self-statements, Diverting Attention, Ignoring Pain Sensations, Increasing Activity Level and Reinterpreting the Pain Sensation, with scores ranging from 0 to 180.

**Statistical analyses**

Statistical analyses were conducted using SPSS (SPSS, Chicago, IL, USA) and AMOS (analysis of moment structures; Small Waters Corp., Chicago, IL, USA). One-way ANOVA (analysis of variance) and post hoc tests were used for group comparisons across time, while within-subjects repeated measures analysis was used to assess individual changes over time. The level of helplessness was found previously to be stable over time, and we therefore measured it at Times 1 and 3 only. For the purpose of analysis, the Time 1 measure was used at Time 2.

**Results**

**Descriptive analysis of clinical and psychological measures**

Table 1 summarizes the demographic, clinical and psychological measurements collected for 157 participants at Time 1, 134 participants at Time 2 and 131 participants at Time 3. The reliability estimates for the scales were assessed by computing the Cronbach α coefficient at Time 1, and were found to be moderate to high.

Overall, these results indicate low physical disability and moderate pain. Likewise, depression, helplessness and coping were found to be within a moderate range. To test the stability of variables over time, one-way ANOVA was used to compare group means across Times 1, 2 and 3. No significant differences were found for the variables over a 12-month period, indicating a stable or well-controlled disease pattern. Repeated-measures within-subjects analysis was conducted to assess individual variations, as opposed to group variations, across time. The only significant difference

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time 1 (Mean, S.D.)</th>
<th>Time 2 (Mean, S.D.)</th>
<th>Time 3 (Mean, S.D.)</th>
<th>Possible range</th>
<th>Cronbach’s α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>57.85 (12.24)</td>
<td>58.52 (11.92)</td>
<td>57.85 (12.24)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA duration (yr)</td>
<td>13.07 (9.45)</td>
<td>13.22 (9.51)</td>
<td>13.09 (9.55)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>MHAQ</td>
<td>0.54 (0.42)</td>
<td>0.51 (0.44)</td>
<td>0.56 (0.52)</td>
<td>0–3</td>
<td>0.83</td>
</tr>
<tr>
<td>AIMS Pain</td>
<td>4.55 (2.29)</td>
<td>4.30 (2.54)</td>
<td>4.47 (2.57)</td>
<td>0–10</td>
<td>0.86</td>
</tr>
<tr>
<td>Psychological</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CES-D</td>
<td>15.94 (11.92)</td>
<td>14.30 (12.14)</td>
<td>14.41 (11.80)</td>
<td>0–60</td>
<td>0.92</td>
</tr>
<tr>
<td>AHI</td>
<td>11.18 (2.86)</td>
<td>11.06 (2.86)</td>
<td>11.06 (2.86)</td>
<td>5–20</td>
<td>0.70</td>
</tr>
<tr>
<td>CSQ-AC</td>
<td>70.37 (33.41)</td>
<td>73.00 (30.69)</td>
<td>72.88 (35.30)</td>
<td>0–180</td>
<td>0.92</td>
</tr>
<tr>
<td>CSQ-PC</td>
<td>21.86 (15.20)</td>
<td>23.03 (16.11)</td>
<td>21.54 (15.50)</td>
<td>0–72</td>
<td>0.85</td>
</tr>
</tbody>
</table>

MHAQ, Modified Health Assessment Questionnaire—Physical Disability; CES-D, Center for Epidemiologic Studies—Depression scale; AHI, Arthritis Helplessness Index—Helplessness subscale; CSQ-AC, Coping Strategies Questionnaire—Active Coping subscale; CSQ-PC, Coping Strategies Questionnaire—Passive Coping subscale; N/A, not applicable.
was detected for depression \((F=4.932, P=0.028)\) which was significantly higher at Time 1 compared with Time 2 and Time 3.

**Cross-sectional analysis of the path model**

A summary of the overall goodness-of-fit statistics of the path models is presented in Table 2. The \(\chi^2\) values at Times 1, 2 and 3 were not significant \((\chi^2=2.673, P=0.263; \chi^2=0.777, P=0.782; \chi^2=3.065, P=0.382)\), which supports the fit of the path model. Various fit indices were used to assess the adequacy of a path model. The goodness-of-fit indexes \((GFI) of 0.993, 1.00 and 0.991 at Times 1, 2 and 3 respectively indicate an excellent fit \((close to 1 in the range 0 –1) at each time point. The root mean square residuals \((RMSEA) of 0.046, 0.000 and 0.013 respectively are within the expected range of unaccounted variance \(<0.05) and represent good closeness of the model fit. The Tucker-Lewis coefficients \((-0.997, 1.010 and 0.999 respectively) and Comparative Fit Index \((1.000, 1.000 and 1.000 respectively) are 1 or close to 1, also indicating a good fit.

The direct, indirect and total effects of paths associated with each independent variable are presented in Table 3. The predicted variance for pain \((R^2=0.52-0.94) was consistently greater than for depression \((R^2=0.37–0.71). The direct effect of physical disability on pain was greater than the indirect effect of passive coping and helplessness at Time 1 and Time 2 but not Time 3, when it was found to be considerably lower. The direct effect of physical disability on depression was only evident at Time 2 and was lower than the indirect effect, with a particularly significant contribution of passive coping \((R^2=0.11).\)

In terms of the indirect effects, helplessness was consistently a stronger predictor of pain, while passive coping was a stronger predictor of depression. Across the three time measure points, depression and pain had a mutual effect on each other at Time 1, followed by pain affecting depression at Time 2, and no relationship between the two outcome factors at Time 3, indicating an inconsistent interaction.

The impact of passive coping was further explored by entering the two subscales \((Catastrophizing and Praying and Hoping) separately into the path analysis to establish which subscale made a greater contribution to the predictive model. At Time 1 each subscale could maintain the significance of the model \((\chi^2=2.590, P=0.274; \chi^2=1.726, P=0.422). but the path between Praying and Hoping and depression was not significant. At Time 2 both Catastrophizing and Praying and Hoping could maintain the significance of the model on their own \((\chi^2=2.769, P=0.096; \chi^2=0.418, P=0.518). At Time 3, however, the path model remained significant only with the Catastrophizing subscale \((\chi^2=0.968, P=0.809). Praying and Hoping could not maintain the fit to the model \((\chi^2=21.303, P < 0.0001).\)

**Longitudinal analysis of the path model**

The strength of the hypothesized path model was further tested in longitudinal analyses across the three time points. The path model at Time 1 was used to predict

---

**Table 2. Cross-sectional (Times 1, 2 and 3) and longitudinal path model (Time 1 to Time 2, Time 2 to Time 3 and Time 1 to Time 3) statistics for 157 participants**

<table>
<thead>
<tr>
<th>Time point</th>
<th>(\chi^2)</th>
<th>(P)</th>
<th>d.f.</th>
<th>GFI</th>
<th>AIC</th>
<th>CMIN</th>
<th>RMSEA</th>
<th>TLI</th>
<th>CFI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-sectional statistics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 1</td>
<td>2.673</td>
<td>0.263</td>
<td>2</td>
<td>0.993</td>
<td>28.67</td>
<td>2.67</td>
<td>0.046</td>
<td>-0.997</td>
<td>1.000</td>
</tr>
<tr>
<td>Time 2</td>
<td>0.077</td>
<td>0.782</td>
<td>1</td>
<td>1.000</td>
<td>28.07</td>
<td>0.07</td>
<td>0.000</td>
<td>1.010</td>
<td>1.000</td>
</tr>
<tr>
<td>Time 3</td>
<td>3.065</td>
<td>0.382</td>
<td>3</td>
<td>0.991</td>
<td>27.065</td>
<td>3.065</td>
<td>0.013</td>
<td>0.999</td>
<td>1.000</td>
</tr>
<tr>
<td>Longitudinal statistics (T1, Time 1; T2, Time 2; T3, Time 3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 to T2</td>
<td>3.460</td>
<td>0.326</td>
<td>3</td>
<td>0.991</td>
<td>37.460</td>
<td>3.460</td>
<td>0.031</td>
<td>0.998</td>
<td>1.000</td>
</tr>
<tr>
<td>T1 to T3</td>
<td>3.071</td>
<td>0.381</td>
<td>3</td>
<td>0.992</td>
<td>37.071</td>
<td>3.071</td>
<td>0.012</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>T2 to T3</td>
<td>0.504</td>
<td>0.777</td>
<td>2</td>
<td>1.000</td>
<td>36.504</td>
<td>0.504</td>
<td>0.000</td>
<td>1.010</td>
<td>1.000</td>
</tr>
</tbody>
</table>

AIC, Akaike Information Criterion; CMIN, Minimum Discrepancy Function; TLI, Tucker–Lewis coefficient; CFI, comparative fit index; GFI, goodness of fit index; d.f., degrees of freedom.

**Table 3. Cross-sectional path analyses: direct, indirect and total effects at Times 1, 2 and 3 for 157 participants**

<table>
<thead>
<tr>
<th>Path</th>
<th>Time 1</th>
<th>Time 2</th>
<th>Time 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>MHAQa (\rightarrow) pain</td>
<td>0.53</td>
<td>0.35</td>
<td>0.25</td>
</tr>
<tr>
<td>MHAQa (\rightarrow) depression</td>
<td>0.41</td>
<td>0.18</td>
<td>0.34</td>
</tr>
</tbody>
</table>

All paths significant at \(P < 0.05.\)

\(a\)Physical Disability subscale.
pain and depression at Time 2 and Time 3. The path model at Time 2 was also used to predict pain and depression at Time 3. Statistically significant path coefficients for each of these tests are presented in Figs 1, 2 and 3.

A summary of the overall goodness-of-fit statistics of the path models is presented in Table 4. The $\chi^2$ value at each prediction point (Time 1 to Time 2; Time 1 to Time 3; and Time 2 to Time 3) was not significant ($\chi^2 = 3.460, P = 0.326; \chi^2 = 3.071, P = 0.381; \chi^2 = 0.504, P = 0.777$), which supports the fit of the path model. The GFI was close to 1 (0.991, 0.992, 1.000), which indicates an excellent fit. The RMSEA was below the expected level of unaccounted variance (<0.05) (0.031, 0.012, 0.000), which represents good closeness of the model fit. The Tucker–Lewis coefficient (0.998, 1.000, 1.010) and comparative fit index (1.000, 1.000, 1.000) provide further support for a good fit of the path models.

The direct, indirect and total effects of independent variables on pain and depression are presented in Table 4. Although they are not as large as those identified in cross-sectional analyses, they are nevertheless considerable. The Time 1 model accounted for 39% of the variance of pain and 25% of the variance of depression at Time 2. The Time 1 model also accounted for 29% of the variance of pain and 21% of the variance of depression at Time 3. Furthermore, the Time 2 model accounted for 43% of the variance of pain and 33% of the variance of depression at Time 3.

As in the cross-sectional analyses, while the essence of the model was maintained some variations were identified. The Time 1 to Time 2 analysis found passive coping only a weak predictor of pain. The Time 1 to Time 3 analysis found a weak direct effect of physical disability on pain. The Time 2 to Time 3 analysis, unlike the previous two analyses, had a direct path between physical disability and passive coping, as in the hypothesized model.

**Discussion**

Extensive testing of a hypothesized biopsychosocial model was undertaken with three cross-sectional analyses and three longitudinal analyses over a period of 12 months. The model, notwithstanding some minor variations, was found to significantly predict pain and depression. Cross-sectionally, it accounted for a large
proportion of the variance of pain (ranging from 52 to 94%) and of depression (from 37 to 71%). Longitudinally, the hypothesized model accounted for between 29 and 43% of the variance of pain and 21 and 33% of the variance of depression. These results indicate that the key factors identified in the hypothesized model—physical disability, helplessness and passive coping—are significant contributors to the levels of pain and depression experienced in RA.

Physical disability as an indicator of the RA disease was the most significant predictor of pain. However, it contains both physical and psychological elements. This may explain why the loss of valued activities is closely linked to depression [14]. Escalante and del Rincon [26] found that 33% of the physical disability score could be explained by the disease characteristics (duration, ESR, articular signs and symptoms and performance-based functional limitations) while 20% was due to psychological status (helplessness and self-efficacy) and symptoms of depression. Another study, however, found physical disability to be better explained by pain (41%) than by radiographic damage (7%) or depression (5%) [27]. This lack of clarity as to the representative value of physical disabilities should be addressed in future studies using more objective clinical indicators, such as ESR, joint count and radiographic status.

A particularly interesting finding emerged in terms of the mediating, psychological factors. Helplessness was a stronger predictor of pain than passive coping. It seems that the perception that one has no control over one’s disease can affect the levels of pain, which have both physical and psychological features. Helplessness affected depression indirectly through passive coping and pain. Similar results were reported in other longitudinal studies, which has found helplessness to mediate the relationship between disease severity and depression [16, 28, 29] and to lead to passive coping with pain and depression [30]. Helplessness has also been reported to mediate the relationship between education level and mortality in RA [31] and influence the effectiveness of medical therapy [32]. Helplessness appears to be modifiable with cognitive–behavioural and educational interventions but it is not clear if such interventions will lead to long-term improvements in health outcomes [31].

Passive coping, although a significant predictor of pain, had a greater impact on the levels of depression compared with helplessness. Thus, it is the passive and negative cognitive processes and behavioural inactivity that may result in higher levels not only of pain but also of depression. Furthermore, by identifying specific passive coping strategies it became evident that catastrophizing in particular is a detrimental factor. Similar results have been reported in other studies [33, 34]. The relationship between catastrophizing and pain was explored in a 30-day daily pain diary study, which found catastrophizing to be associated with more accurate recall of pain intensity [35]. The authors suggest that this may be due to an increase in somatic awareness or exaggeration of actual and recalled pain, which can affect the effectiveness of treatment. Praying and hoping, although considered to be a passive and therefore maladaptive coping strategy, was not consistent a predictor of pain and depression as catastrophizing. This may be because praying can be experienced as an active means of seeking and receiving social support through spiritual activities [36]. The importance of coping in adjustment to RA should not be underestimated. Passive, maladaptive coping has qualities that outweigh the benefits of active coping [23], lead to more pain and depression [6, 7, 37] and withdrawal from employment [38].

How do the findings of this study compare with those of other recent studies? Although the proposed model consists of variables identified in previous studies, the relationship between these variables is explained more comprehensively. The recent studies reviewed above [3, 4, 6, 8–12], with the exception of two [5, 7], used multiple regression analyses to determine the predictors of pain, depression, stress, cognitive functioning or physical disability with reference to RA. Thus, they can only refer to a linear impact of a group of independent variables on the dependent variables. Path analysis, however, provides a more interactive picture of the relationship between independent variables in their prediction of the dependent variables and even the relationship between dependent variables, such as depression and pain, in this study. Consequently, the proposed and tested model is a sound illustration of the biopsychosocial perspective on RA.

These findings have significant implications for RA management. Intervention should focus on reducing passive coping, and perhaps catastrophizing in particular, in order to manage depression in RA. The

<table>
<thead>
<tr>
<th>Path</th>
<th>Direct path</th>
<th>Indirect path</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>MHAQ$^a$ → Pain</td>
<td>0.24</td>
<td>0.15</td>
<td>0.39</td>
</tr>
<tr>
<td>MHAQ$^a$ → Depression</td>
<td>–</td>
<td>0.25</td>
<td>0.25</td>
</tr>
</tbody>
</table>

All paths significant at $P < 0.05$.

$^a$Physical Disability subscale.
findings of this study also suggest that close attention needs to be given to the level of helplessness when targeting pain reduction.

Some limitations of this study should be noted. First, the hypothesized model is only one possible causal model of complex biopsychosocial interaction in the experience of RA. Secondly, physical disability is only a partial indicator of clinical activity in RA. Thirdly, 12 months is a relatively short time in the lifetime of RA disease and thus offers a limited longitudinal perspective. However, stable physiological and psychological outcomes have been reported in studies of longer duration [8, 12] (2 and 5 yr respectively).

Noteworthy features of this study include a methodologically sound and comprehensive causal model. Secondly, the relatively large sample size is representative of the RA population in terms of gender, age and other demographic characteristics. Thirdly, the hypothesized model lends itself to clinical application. Fourthly, this study provides a fine distinction between the role of passive coping and helplessness in pain and depression as well as the degree of maladaptiveness of passive coping, catastrophizing being a more consistently detrimental predictor of pain and depression compared with praying and hoping.

In summary, this study offers strong support for the notion that RA needs to be considered from a biopsychosocial approach, in which the physical aspect of the disease may dominate but is mediated by psychological factors that, given attention, can be targeted with an appropriate intervention. By doing so, better health outcomes may be achieved for RA patients.

**Conflict of interest**

The authors have declared no conflicts of interest.

**References**


