SUPPLEMENTARY MATERIAL

SEVEN-YEAR TOLERABILITY PROFILE OF GLUCOCORTICOIDS USE IN EARLY RHEUMATOID ARTHRITIS: DATA FROM THE ESPOIR COHORT

Camille Roubille\textsuperscript{1,2}, Nathalie Rincheval\textsuperscript{1,3}, Maxime Dougados\textsuperscript{4}, René-Marc Flipo\textsuperscript{5}, Jean-Pierre Daurès\textsuperscript{3}, Bernard Combe\textsuperscript{1}.

Supplementary Methods 1: Design of the ESPOIR cohort:

The ESPOIR cohort is a French prospective observational cohort including patients with early arthritis who were enrolled between 2002 and 2005, within 6 months of symptoms onset, were naïve to DMARDs and GC therapy, and had RA or undifferentiated arthritis with the potential for progression to RA.

All included patients were evaluated every 6 months for the first 2 years, then once a year. Some clinical, biological, functional and radiographic data were recorded. In particular, at baseline and at each visit, medical history, physical examination data (including weight, height, blood pressure, and rheumatologic assessment), and data on comorbidities (including CVD, smoking status, infection, fracture) were collected as well as data on biological variables (including C reactive protein [CRP], lipids and blood glucose levels) measured using standard methods in local laboratories. Rheumatologist treatment followed the standard of care.

Supplementary Methods 2: Excluded patients who dropped out within the first year:

Among the 48 patients who dropped out within the first year, 20 patients underwent only the inclusion visit before they dropped out, and had no GC treatment, given that patients had to be naïve to GC to be included. Among the 28 remaining patients, 4 patients were excluded by the physician (other diagnosis than RA or UA) and 24 patients were lost of follow-up, with no data about their outcomes or their treatment (GC or not).
Supplementary Table S1: distribution of patients according to glucocorticoid (GC) treatment duration

<table>
<thead>
<tr>
<th>Total cumulative GC duration</th>
<th>duration</th>
<th>Frequency</th>
<th>Percent</th>
<th>Cumulative Frequency</th>
<th>Cumulative Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-06 m</td>
<td>73</td>
<td>18.96</td>
<td>73</td>
<td>18.96</td>
</tr>
<tr>
<td></td>
<td>06-12 m</td>
<td>40</td>
<td>10.39</td>
<td>113</td>
<td>29.35</td>
</tr>
<tr>
<td></td>
<td>12-18 m</td>
<td>39</td>
<td>10.13</td>
<td>152</td>
<td>39.48</td>
</tr>
<tr>
<td></td>
<td>18-24 m</td>
<td>33</td>
<td>8.57</td>
<td>185</td>
<td>48.05</td>
</tr>
<tr>
<td></td>
<td>24-36 m</td>
<td>40</td>
<td>10.39</td>
<td>225</td>
<td>58.44</td>
</tr>
<tr>
<td></td>
<td>36-48 m</td>
<td>30</td>
<td>7.79</td>
<td>255</td>
<td>66.23</td>
</tr>
<tr>
<td></td>
<td>48-60 m</td>
<td>32</td>
<td>8.31</td>
<td>287</td>
<td>74.55</td>
</tr>
<tr>
<td></td>
<td>60-72 m</td>
<td>29</td>
<td>7.53</td>
<td>316</td>
<td>82.08</td>
</tr>
<tr>
<td></td>
<td>72-84 m</td>
<td>69</td>
<td>17.92</td>
<td>385</td>
<td>100.00</td>
</tr>
</tbody>
</table>
Supplementary Figure S1: Covariates selection (principal analysis, n=602)

First set of covariates related to the outcome:
gender, age (>50.1), GC (Y/N), NSAID (Y/N), fibrate and statin (Y/N),
antithrombotic treatment (Y/N), BMI (BMI>24.2), obesity (BMI>30),
SJC (>6), TJC (>7), DAS28-CRP (4 levels), DAS28-CRP (>4.7),
HAQ (>0.9), smokers (Y/N), cardiovascular risk (Y/N),
hypercholesterolemia (Y/N), diabetes (Y/N), CRP (>10 mg/l),
RF IgA (>9 UI/ml), RF IgM (>9 UI/ml), ACPA (>50 UI/ml),
typical erosion (Y/N), erosion vSIS score (>0), JSN vSIS score (>2),
modified total Sharp score (>2)

Log rank test (p-value<0.15):
age, gender, diabetes, hypertension, HAQ, ACPA

Chi-square test (p-value<0.15):
DAS28-CRP (4 levels), VAS patient, HAQ, CRP, ACPA, SJC, TJC,
diabetes, smokers, ESR, modified total Sharp score, RF IgA, cardiovascular risk

Covariates included in PS logistic-regression model (p-value<0.05):
age, gender, diabetes, hypertension, HAQ, ACPA, SJC, TJC,
patient VAS, CRP, ESR, smokers, modified total Sharp score,
RF IgA, cardiovascular risk

Covariates retained in the final PS logistic-regression model:
ACPA, diabetes, HAQ, modified total Sharp score, cardiovascular risk, VAS patient

Weighted COX proportional-hazards model with IPTW (p-value<0.05):
age, gender, hypertension, GC (Y/N)

ACPA, anti-citrullinated protein antibody; BMI, body mass index; CRP, C-reactive protein; DAS28-CRP, disease activity score 28 using CRP; ESR, erythrocyte sedimentation rate; GC, glucocorticoid; HAQ, health assessment questionnaire; IPTW, inverse-probability-of-treatment weighting technique; JSN, joint space narrowing; NSAIDs, non-steroidal anti-inflammatory drugs; PS, propensity score; RF, rheumatoid factor; SJC, swollen joint count; TJC, tender joint count; mSHS, van der Heijde-modified total Sharp Score; VAS, patient’s overall assessment using visual analogue scale; Y/N, yes or no.
Supplementary Figure S2: Covariates selection for the subsequent analysis, n=657 (comprising the 602 patients without history and the 55 patients with history and sufficient data)

First set of covariates related to the outcome:
- gender, age (>50.1), GC (Y/N), NSAID (Y/N),
- fibrate and statin (Y/N), antiplatelet agent (Y/N), BMI (>24.2),
- obesity (BMI>30), SJC (>6), TJC (>7), DAS28-CRP (4 levels),
- DAS28-CRP (>4.7), HAQ (>0.9), smokers (Y/N), cardiovascular risk (Y/N), hypertension (Y/N), hypercholesterolemia (Y/N), diabetes (Y/N),
- CRP (>10 mg/l), RF IgA (>9 U/ml), RF IgM (>9 U/ml), ACPA (>50 U/ml),
- typical erosion (Y/N), erosion vSHS score (>0), JSN vSHS score (>2),
- modified total Sharp score (>2), history of CVD or severe infections or fractures

Log rank test (p-value=0.15):
- age, gender, diabetes, obesity, hypertension, HAQ, RF IgM, CRP, ACPA, history

Second set of covariates related to GC :
- gender, age (>50.1), fibrate and statin (Y/N), antiplatelet agent (Y/N), VAS patient (>65), HAQ (>0.9), CRP (>10 mg/l), obesity (BMI>30),
- cardiovascular risk (Y/N), hypertension (Y/N), hypercholesterolemia (Y/N),
- DAS28-CRP (4 levels), DAS28-CRP (>4.7), SJC (>6), TJC (>7),
- diabetes (Y/N), smokers (Y/N), ESR (>28 mm), RF IgA (>9 U/ml),
- RF IgM (>9 U/ml), ACPA (>50 U/ml), typical erosion (Y/N),
- erosion vSHS score (>0), JSN vSHS score (>2), modified total Sharp score (>2)

Chi-square test (p-value=0.15):
- DAS28-CRP (4 levels), DAS28-CRP (>4.7), VAS patient, HAQ, CRP, ACPA, SJC, TJC,
- diabetes, smokers, ESR, RF IgA, cardiovascular risk

Covariates included in PS logistic-regression model (p-value=0.05):
- age, gender, diabetes, obesity, hypertension, HAQ, ACPA, SJC, TJC, patient VAS, CRP, ESR, smokers,
- RF IgA, RF IgM, cardiovascular risk, history

Weighted Cox proportional-hazards model with IPTW (p-value=0.05):
- age, gender, obesity, hypertension, history, RF IgM, CRP, GC (Y/N)

ACPA, anti-citrullinated protein antibody; BMI, body mass index; CRP, C-reactive protein; DAS28-CRP, disease activity score 28 using CRP; CVD, cardiovascular diseases; ESR, erythrocyte sedimentation rate; GC, glucocorticoid; HAQ, health assessment questionnaire; IPTW, inverse-probability-of-treatment weighting technique; JSN, joint space narrowing; NSAIDs, non-steroidal anti-inflammatory drugs; PS, propensity score; RF, rheumatoid factor; SJC, swollen joint count; TJC, tender joint count; mSHS, van der Heijde-modified total Sharp Score; VAS, patient’s overall assessment using visual analogue scale; Y/N, yes or no.
Supplementary Figure S3: Distribution of cumulative glucocorticoid (GC) dose
### Supplementary Table S2: Stratified Cox model based on cumulative GC dose and on duration of GC treatment levels:

#### Stratified Cox model based on cumulative dose (quartiles)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DF</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>Chi-Square</th>
<th>Pr &gt; ChiSq</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>1</td>
<td>0.48155</td>
<td>0.20958</td>
<td>5.2795</td>
<td>0.0216</td>
<td>1.619</td>
<td>1.073, 2.441</td>
</tr>
<tr>
<td>gender</td>
<td>M</td>
<td>0.61218</td>
<td>0.20068</td>
<td>9.3057</td>
<td>0.0023</td>
<td>1.844</td>
<td>1.245, 2.733</td>
</tr>
<tr>
<td>hypertension</td>
<td>1</td>
<td>0.42695</td>
<td>0.22364</td>
<td>3.6445</td>
<td>0.0563</td>
<td>1.533</td>
<td>0.989, 2.376</td>
</tr>
</tbody>
</table>

#### Stratified Cox model based on duration of GC treatment levels (quartiles)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DF</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>Chi-Square</th>
<th>Pr &gt; ChiSq</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>1</td>
<td>0.49177</td>
<td>0.21047</td>
<td>5.4595</td>
<td>0.0195</td>
<td>1.635</td>
<td>1.082, 2.470</td>
</tr>
<tr>
<td>gender</td>
<td>M</td>
<td>0.60531</td>
<td>0.19960</td>
<td>9.1972</td>
<td>0.0024</td>
<td>1.832</td>
<td>1.239, 2.709</td>
</tr>
<tr>
<td>hypertension</td>
<td>1</td>
<td>0.40211</td>
<td>0.22334</td>
<td>3.2415</td>
<td>0.0718</td>
<td>1.495</td>
<td>0.965, 2.316</td>
</tr>
</tbody>
</table>