

## CONCISE REPORT

# Safety of synthetic and biological DMARDs: a systematic literature review informing the 2016 update of the EULAR recommendations for management of rheumatoid arthritis

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## ABSTRACT

**Objectives** To assess the safety of synthetic (s) and biological (b) disease-modifying antirheumatic drugs (DMARDs) for the management of rheumatoid arthritis (RA) to inform the European League Against Rheumatism recommendations for the management of RA.

**Methods** Systematic literature review (SLR) of observational studies comparing any DMARD with another intervention for the management of patients with RA. All safety outcomes were included. A comparator group was required for the study to be included. Risk of bias was assessed with the Hayden's tool.

**Results** Twenty-six observational studies addressing diverse safety outcomes of therapy with bDMARDs met eligibility criteria (15 on serious infections, 4 on malignancies). Substantial heterogeneity precluded meta-analysis. Together with the evidence from the 2013 SLR, based on 15 studies, 7 at low risk of bias, patients on bDMARDs compared with patients on conventional sDMARDs had a higher risk of serious infections (adjusted HR (aHR) 1.1 to 1.8)—without differences across bDMARDs—a higher risk of tuberculosis (aHR 2.7 to 12.5), but no increased risk of infection by herpes zoster. Patients on bDMARDs did not have an increased risk of malignancies in general, lymphoma or non-melanoma skin cancer, but the risk of melanoma may be slightly increased (aHR 1.5).

**Conclusions** These findings confirm the known safety pattern of bDMARDs, including both tumour necrosis factor- $\alpha$  inhibitor (TNFi) and non-TNFi, for the treatment of RA.

## INTRODUCTION

The armamentarium nowadays available for the treatment of patients with rheumatoid arthritis (RA) is impressive and has substantially expanded in the last decades. A plethora of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biological DMARDs (bDMARDs) and more recently also targeted synthetic DMARDs (tsDMARDs), which can be used in different sequences and/or combinations, is at the disposal of rheumatologists to offer to patients. This, naturally,

also implies choices to be made when deciding on the best treatment for a particular patient.

Treatment decisions, particularly in the case of patients with RA with insufficient response to a first csDMARD, are mainly made based on the expected efficacy of a drug.<sup>1</sup> However, there are no important differences in efficacy across bDMARDs and tsDMARDs.<sup>2–3</sup> Therefore, other aspects among which safety may have a more prominent place in decision-making.<sup>1</sup> While short-term safety is addressed in clinical trials, it is long-term safety that we are primarily interested in when making our decisions. Observational studies (eg, cohort studies, registries) provide us with more relevant information since, unlike clinical trials, they include a non-selected group of patients, are representative of daily clinical practice and cover a longer period of time.<sup>4</sup>

In order to inform the task force responsible for the 2016 update of the European League Against Rheumatism (EULAR) RA management recommendations, we performed a systematic literature review (SLR) to update the evidence for the safety of csDMARDs, tsDMARDs and bDMARDs in patients with RA.<sup>5</sup> This SLR is an update of the SLR performed previously for the corresponding 2013 update of the RA management recommendations.<sup>6</sup> The results of this and two other SLRs<sup>2–3</sup> provided the task force with the current state of evidence.

## METHODS

### Literature search

The search was performed in MEDLINE, EMBASE and The Cochrane CENTRAL Register of Controlled Trials (Central), until 9 March 2016, without language restrictions. All newly included studies were published from 2013 onwards, as an update of the previous SLR.<sup>6</sup> As this SLR is an update of the 2013 SLR,<sup>6</sup> results are shown together to give a more complete overview on the safety of DMARDs. Details on complete search strategies are provided in online supplementary material. References from included studies were also screened.

The literature search addressed the safety of DMARDs. The research questions were structured

according to a PICO format (Patients, Intervention, Comparator and Outcomes) and eligible study types were defined.<sup>7</sup> Participants were adults (aged  $\geq 18$  years) with a clinical diagnosis of RA. Studies including patients with other diagnoses were eligible only if the results from patients with RA were presented separately. The intervention was any DMARD (csDMARD, bDMARD—including biosimilars—or tsDMARD), including all drugs (methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, gold/auranofin, azathioprine, chlorambucil, chloroquine, ciclosporin, cyclophosphamide, mycophenolate, minocycline, penicillamine, tacrolimus, anakinra, infliximab, etanercept, adalimumab, rituximab (RTX), abatacept, tocilizumab, golimumab, certolizumab pegol or tofacitinib), formulations and duration). Glucocorticoids were also included. The comparator was a(nother) bDMARD, sDMARD, glucocorticoid, combination therapy or the general population. Studies were only eligible if they included a comparator group, as a formal comparison is the only insightful manner to take any conclusions about safety. All safety outcomes were considered, namely infections (including serious infections, opportunistic infections such as tuberculosis and herpes zoster), malignancies, mortality, cardiovascular disease, change in lipid levels, impairment in renal function, elevation of liver enzymes, haematological abnormalities, gastrointestinal effects, demyelinating disease, induction of autoimmune disease and teratogenicity. Only observational studies were included, namely cohort studies/registries and study series with  $>30$  cases.

### Selection of studies, data extraction and assessment of risk of bias

Two reviewers (SR and AS) independently screened titles and abstracts, and if necessary the full-text, for eligibility. In cases of disagreement, a third reviewer (RBML) was involved. Data from eligible studies were extracted regarding study and population characteristics, inclusion and exclusion criteria, follow-up time, interventions, outcome definition and outcome measures using a standardised data extraction form.

The two reviewers independently assessed the risk of bias of each included study using the 'Hayden-tool', which evaluates the following items: participation, attrition, prognostic factor measurement, outcome measurement, confounding and analysis.<sup>8</sup>

### RESULTS

In total and after de-duplication, 4436 references were obtained, of which 26 studies were included (flowchart in online supplementary figure S1). All studies included patients on bDMARDs and only one study also addressed a comparison between csDMARDs.<sup>9</sup> There were no eligible studies on tsDMARDs or glucocorticoids. Of the included studies, 15 studies focused on infections,<sup>10–24</sup> 4 on malignancies,<sup>9 25–27</sup> 1 on mortality,<sup>28</sup> 4 on cardiovascular events<sup>29–32</sup> and 2 on interstitial lung disease.<sup>33 34</sup> Details can be found in tables 1–3 and online supplementary tables S1–S57.

Studies were very heterogeneous in every single item of the PICO, thus precluding data-pooling (meta-analysis), and results are presented descriptively.

Of the newly included 11 studies addressing serious infections, 6 compared patients on bDMARDs with those on csDMARDs or with the general population,<sup>10–15</sup> whereas 8 studies<sup>10–12 16–20</sup> addressed a comparison between different bDMARDs (3 studies addressed both comparisons)<sup>10–12</sup>—tables 1 and 2. In total, and considering the previous evidence from 2013,<sup>6</sup> 15 studies, 7 at low risk of bias, compared the risk of

serious infections between bDMARDs and csDMARDs and overall found a significantly increased risk with adjusted HRs (aHR) between 1.0 and 1.8 per study.<sup>10–15 35–43</sup> More recent studies at low risk of bias did not show an increased risk.<sup>10 14</sup> One study comparing bDMARDs with the general population reported standardised incidence rates of 16–20 for tumour necrosis factor- $\alpha$  inhibitor (TNFi) and even higher for RTX (table 1).<sup>15</sup> In total, six studies,<sup>21 44–48</sup> performed in European and American datasets, of which four were at low risk of bias, focused on the occurrence of herpes zoster, most of them reporting no increased risk for this type of infection in patients on TNFi (no studies for other bDMARDs), particularly the studies at low risk of bias and/or those that had been adjusted for dropouts.<sup>21 44–46</sup>

Seven studies addressing tuberculosis, most of them being at moderate or high risk of bias, showed an increased risk of tuberculosis in patients on TNFi (no studies for other sDMARDs), both compared with the general population and to patients on csDMARDs (aHR 2.7 to 12.5 per study).<sup>11 22 23 49 50</sup>

One study at moderate risk of bias did not show an increased risk of skin infections in patients on TNFi compared with patients on csDMARDs.<sup>24</sup> One study at moderate risk of bias reported no increased risk of non-viral opportunistic infections in patients on TNFi versus csDMARDs.<sup>23</sup>

Concerning comparisons across bDMARDs, eight studies, only one of them being at low risk of bias, compared the risk of serious infections across bDMARDs and in general did not show differences between several drugs.<sup>10–12 16–20</sup> Comparisons included TNFi and non-TNFi, both aggregated in classes and as individual drugs. One of the studies found a signal for a higher risk of serious infections with infliximab compared with etanercept<sup>17</sup> and another for infliximab, etanercept and RTX compared with abatacept<sup>20</sup> (table 2). No differences were found between TNFi and non-TNFi on the risk of herpes zoster.<sup>21</sup>

The overall risk of malignancies was investigated in a total of nine studies, six of them being at low risk of bias (table 3).<sup>9 10 14 25 51–55</sup> Both in comparison to the general population and to patients on csDMARDs, patients on bDMARDs did not show an increased risk for malignancies. In a few more recent studies, patients on non-TNFi were also included.<sup>9 10</sup> Similarly, no increased risk for solid cancers has been found for patients on bDMARDs compared with csDMARDs (two studies were at low risk of bias).<sup>9 26</sup> The same was true for the analysis of the individual solid cancers (eg, breast cancer, lung cancer, colorectal cancer—online supplementary table S37.2). Patients on bDMARDs (five studies, three at low risk of bias, all with TNFi), as compared with the general population, had a higher risk of lymphoma, with adjusted aHRs ranging from 2.3 to 5.9, but in comparison to patients on csDMARDs (three studies, two at low risk of bias), no increased risk was found. In patients on bDMARDs, non-melanoma skin cancer may occur more frequently than in the general population (aHR 1.7; one study at low risk of bias), but compared with csDMARDs, there was no increased risk (four studies, two at low risk of bias). A 'safety alarm signal' was shown for abatacept compared with csDMARDs: a higher risk for its occurrence, with an aHR of 15.3 (95% CI 2.1 to 114), but this 'signal' was only based on two cases.<sup>9</sup> One study at low risk of bias has shown that patients on bDMARDs may have an increased risk for melanoma compared with csDMARDs (aHR 1.5 (95% CI 1.0 to 2.2)).<sup>56</sup>

For the remaining outcomes, the scarcity of data precluded definitive conclusions, but new safety signals were absent (see online supplementary tables S39–S57).

**Table 1** Serious infections in patients on bDMARDs compared with patients on csDMARDs or general population (observational studies)

| Year of publication       | Study ID  | Registry  | Intervention   | Control            | aHR (intervention vs comparator/control)                  | Risk of bias |
|---------------------------|---|---|----------------|--------------------|---|--------------|
| <b>Serious infections</b> |   |   |                |                    |   |              |
| ≤2013                     | Galloway 2011 Rheumatology(a) <sup>35</sup>       | BSRBR   | 3 TNFi         | csDMARDs           | 1.2 (1.1 to 1.5)  | Low          |
|                           | Greenberg 2010 ARD <sup>36</sup>                  | CORRONA   | 3 TNFi+MTX     | MTX                | 1.1 (1.0 to 1.3)  | Low          |
|                           | Grijalva 2011 JAMA <sup>37</sup>                  | Claim database  | 3 TNFi         | csDMARDs           | 1.1 (0.9 to 1.2)  | Moderate     |
|                           | Grijalva 2010 Rheumatology <sup>38</sup>          | Claim database  | 3 TNFi         | MTX                | 1.3 (0.8 to 2.2)  | Moderate     |
|                           | Komano 2011 J Rheum <sup>39</sup>                 | REAL  | ETA/IFX        | csDMARDs           | RR 2.4 (1.1 to 5.1)                                       | Moderate     |
|                           | Sakai 2012 AC&R <sup>40</sup>                     | REAL  | ETA/IFX        | csDMARDs           | RR 2.0 (1.3 to 3.2)                                       | Moderate     |
|                           | Strangfeld 2011 ARD <sup>41</sup>                 | RABBIT  | 3 TNFi         | csDMARDs           | 1.8 (1.2 to 2.7)  | Low          |
|                           | Lane 2011 Medicine (Baltimore) <sup>42</sup>      | Claim database  | 3 TNFi         | csDMARDs           | 1.2 (1.0 to 1.5) vs HCQ, SSZ, gold                        | Moderate     |
|                           | Galloway 2011 Rheumatology (b) <sup>43</sup>      | BSRBR   | Anakinra       | csDMARDs           | 1.6 (0.9 to 2.7)  | Low          |
|                           | Aaltonen 2015 J Rheum <sup>10</sup>               | National Register for Biologic Treatment in Finland (ROB-FIN) | 3 TNFi         | csDMARDs           | 0.9 (0.6 to 1.4)  | Low          |
| 2013–2016                 | Chiu 2014 Int J Rheum Dis <sup>11</sup>           | Taiwan's National Health Insurance Research Database          | RTX            | csDMARDs           | 1.1 (0.6 to 1.9)  | High         |
|                           | Lampopoulos 2015 Clin Exp Rheumatol <sup>12</sup> | Files Laiko University Hospital                               | TNFi (ETA/ADA) | csDMARDs           | 1.0 (0.9 to 1.2)*   | High         |
|                           | Miranda 2014 Rev Colom Rheumatol <sup>13</sup>    | Files Colombian Hospital                                      | bDMARDs (9?)   | csDMARDs           | 6.9 (3.1 to 15.4)   | High         |
|                           | Morgan 2014 Rheumatology <sup>14</sup>            | BSRBR   | bDMARDs†       | csDMARDs           | 2.7 (1.1 to 6.3)  | High         |
|                           | Cobo Ibanez 2014 Rheumatol Int <sup>15</sup>      | BIODASER  | ETA            | csDMARDs           | 1.0 (0.8 to 1.3)  | Low          |
|                           |   |   | 3 TNFi         | General population | ♂ 16 (13–20); ♀ 21 (19–24)                                | Low          |
|                           |   |   | RTX            |                    | ♂ 32 (1–179); ♀ 186 (106–302)                             |              |
|                           |   |   |                |                    |   |              |
|                           |   |   |                |                    |   |              |
|                           |   |   |                |                    |   |              |
| <b>Herpes zoster</b>      |   |   |                |                    |   |              |
| ≤2013                     | Galloway ARD 2013 <sup>44</sup>                   | BSRBR   | 3 TNFi         | csDMARDs           | 1.7 (1.1 to 2.7); adjusted for drop-outs 1.5 (1.0 to 2.4) | Low          |
|                           | McDonald 2009 Clin Inf Diseases <sup>47</sup>     | Claim Database  | 3 TNFi         | csDMARDs           | 1.4 (1.1 to 1.8)  | Moderate     |
|                           | Strangfeld 2009 JAMA <sup>45</sup>                | RABBIT  | 3 TNFi         | csDMARDs           | 1.6 (1.0 to 2.7)  | Low          |
|                           | Garcia-Doval 2010 ARD <sup>48</sup>               | BIODASER  | TNFi (3?)      | General population | 10 (3 to 26)  | Low          |
|                           | Winthrop 2013 JAMA <sup>46</sup>                  | Claim Database  | 3 TNFi         | csDMARDs           | 1.0 (0.8 to 1.3)  | Moderate     |
|                           | Pappas 2015 AC&R <sup>21</sup>                    | CORRONA   | csDMARDs       | TNFi               | 1.4 (0.8 to 2.3)  | Low          |
|                           |   |   |                |                    |   |              |
|                           |   |   |                |                    |   |              |
|                           |   |   |                |                    |   |              |
|                           |   |   |                |                    |   |              |
| <b>Tuberculosis</b>       |   |   |                |                    |   |              |
| ≤2013                     | Dixon 2010 ARD(a) <sup>66</sup>                   | BSRBR   | 3 TNFi         | csDMARDs           | NR  | Low          |
|                           | Tam 2010 Clin Exp Rheumatol <sup>49</sup>         | Hong Kong Cohort  | 3 TNFi         | General population | 34.9 (8.9 to 137.2)                                       | Moderate     |
|                           |   |   |                | csDMARDs           | 12.5 (3.5 to 44.7)  |              |
|                           | Tubach 2009 A&R <sup>50</sup>                     | RATIO   | 3 TNFi         | General population | 12.4 (9.1 to 16.9)  | Low          |
|                           | Winthrop ARD <sup>67</sup>                        | Claim database  | 3 TNFi         | General population | NR  | Moderate     |
|                           | Ke 2013 Tuberc Lung Dis <sup>22</sup>             | Taiwan's National Health Insurance Research Database          | TNFi (ADA/ETA) | csDMARDs           | 4.9 (2.1 to 11.1)   | Moderate     |
|                           | Baddley 2014 ARD <sup>23</sup>                    | 4 US insurance datasets—SABER study (claims dataset)          | 3 TNFi         | csDMARDs           | 4.2 (0.5 to 33.5)   | Moderate     |
|                           | Chiu 2014 Int J Rheum Dis <sup>11</sup>           | Taiwan's National Health Insurance Research Database          | TNFi (ADA/ETA) | csDMARDs           | 2.7 (2.1 to 3.3)  | High         |
|                           |   |   |                |                    |   |              |
|                           |   |   |                |                    |   |              |
| <b>Skin infections</b>    |   |   |                |                    |   |              |
| 2013–2016                 | Wasson 2013 BMC Infect Dis <sup>24</sup>          | US Veterans (Claims database)                                 | 3 TNFi         | csDMARDs           | 1.1 (0.6 to 2.0)§   | Moderate     |

Continued

**Table 1** Continued

| Year of publication                             | Study ID                       | Registry   | Intervention                | Control  | aHR (intervention vs comparator/control)                                     | Risk of bias |
|---|--------------------------------|--|-----------------------------|----------|--|--------------|
| Non-viral opportunistic infections <sup>¶</sup> |                                |  |                             |          |  |              |
| 2013–2016                                       | Baddley 2014 ARD <sup>23</sup> | 4 US insurance datasets (SABER study (claims dataset)) | 3 TNFi<br>ADA<br>ETA<br>IFX | csDMARDs | 1.6 (0.9 to 3.1)<br>1.8 (0.6 to 5.3)<br>0.8 (0.4 to 1.8)<br>2.6 (1.2 to 5.6) | Moderate     |

Estimates in bold reflect a risk/ratio statistically significantly different from 1, ie association is statistically significant.

More details are found in online supplementary tables S1–S31.

\*Unadjusted estimate; no adjusted estimate reported.

†ADA, ABA, ETA, RTX, TCZ, IFX.

#Standardised incidence rates are reported, with the general population as the reference.

\$Adjusted OR reported.

¶Non-viral opportunistic infections included fungal infections, tuberculosis, pneumocystosis, nocardiosis/actinomycosis, non-tuberculous mycobacteria, salmonellosis, listeriosis and legionellosis.

ADA, adalimumab; aHR, adjusted Hazard Ratio; bDMARDs, biological disease-modifying antirheumatic drugs; BIOBADASER, Spanish Biologics Register; BSRBR, British Society of Rheumatology Biologics Register; CORONA, Consortium of Rheumatology Researchers of North America; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; C2P, certolizumab; ETA, etanercept; HCQ, hydroxychloroquine; IFX, infliximab; MTX, methotrexate; NR, not reported; RABBIT, Rheumatoid Arthritis Observation of Biologic Therapy (in German); RATIO, French Biologics Register; REAL, Registry of Japanese Rheumatoid Arthritis Patients for Long-term Safety; RR, relative risk; RTX, rituximab; SSZ, sulfasalazine; TCZ, tocilizumab; TNFi, tumour necrosis factor  $\alpha$  inhibitor.

## DISCUSSION

Existing literature has further confirmed that patients on bDMARDs (both TNFi and non-TNFi) have an increased risk of serious infections compared with patients on csDMARDs and that in general there are no differences across bDMARDs. There is an increased risk for tuberculosis with TNFi, whereas this has not been studied well for non-TNFi. There does not seem to be an increased risk of herpes zoster with bDMARDs. In addition, bDMARDs are not associated with an increased risk of malignancies, with the potential exception of melanoma, based on one study only.

Interestingly, more recent studies addressing serious infections, and especially those at low risk of bias, did not show an increased risk of infections anymore.<sup>10 14</sup> This contrasts with earlier studies addressing the same outcome, in which a higher risk of infections had been reported consistently even in those at low risk of bias.<sup>35 36 41</sup> This effect may reflect a change in the attitude of physicians who now more carefully screen and monitor patients (including infection prophylaxis, when indicated) and treat infections in patients on bDMARDs appropriately.

In general, our conclusions are in line with those drawn in 2013,<sup>6</sup> which is reassuring. The accumulating body of evidence related to bDMARDs is consistently showing us that patients with RA can be treated in a relatively safe way with these drugs. This SLR extends these conclusions also to non-TNFi bDMARDs, which was not possible in the previous SLR.<sup>6</sup> Still, most literature on safety pertains to TNFi, and we need more studies including non-TNFi bDMARDs and tsDMARDs in future.

This SLR also highlights the importance of observational studies in addressing safety aspects of treatment, particularly those studies that include a comparator and truly allow us to assign risks to patients on a particular intervention (eg, bDMARDs). Without a proper comparison, it is impossible to truly judge risks. In addition, these are studies that include all types of patients and follow them up for a long period of time, directly reflecting daily clinical practice, which increases their generalisability.<sup>4</sup> This is what we need to get better insight into safety aspects of treatments as it complements the limited information derived from clinical trials. Admittedly, conducting this type of analysis in observational studies properly is challenging.<sup>57</sup> Several confounders can influence the relationships of interest, and they need to be carefully considered. Even though this is done, even the ‘best comparator’ that we at the moment have to contrast safety of bDMARDs with, namely csDMARDs, also implies challenges and limitations, as we know that patients on csDMARDs have less severe disease, or sometimes historical data are used for comparison purposes, which also introduces some sources of bias. Increasingly complex analyses are being undertaken to circumvent the known challenges, for example, analysis adjusted for propensity score.<sup>58</sup> Collaborations between registries are important in order to homogenise procedures, raise the overall quality and allow comparisons, and these should be encouraged.<sup>59</sup> This will lead to better information for clinicians and better care to patients. Over and above the current data from observational studies, other information previously obtained through randomised clinical trials (RCTs) or addressed in package inserts should be taken into account. The labels of each drug, including adverse events and lab monitoring, remain undisputed and it is good practice to follow them.

Although this SLR aimed at including all DMARDs, the eligible studies were only on bDMARDs. This points to the need



**Table 2** Serious infections in patients on bDMARDs, comparison between different bDMARDs (observational studies)

| Year of publication                 | Study ID   | Registry  | Intervention                                  | Control                     | aHR (intervention vs comparator/control) | Risk of bias |
|-------------------------------------|--|---|---|-----------------------------|--|--------------|
| Serious Infections                  |  |   |   |                             |  |              |
| 2013–2016                           | Aaltonen 2015 J Rheum <sup>10</sup>                | National Register for Biologic Treatment in Finland (ROB-FIN) | RTX   | TNFi                        | 1.4 (0.8 to 2.6)                         | Low          |
|                                     | Chiang 2014 Comp methods <sup>16</sup>             | Taiwan's National Health Insurance Research Database          | ETA   | ADA                         | 2.0 (1.1 to 3.6)*                        | High         |
|                                     | Chiu 2014 Int J Rheum Dis <sup>11</sup>            |   | ADA   | ETA                         | 1.8 (1.2 to 2.8)                         | High         |
|                                     | Curtis 2014 AC&R <sup>17</sup>                     | US Veterans (claims dataset)                                  | ABA   | ETA                         | 1.1 (0.6 to 2.1)                         | Moderate     |
|                                     |  |   | ADA   |                             | 1.4 (0.9 to 2.2)                         |              |
|                                     |  |   | IFX   |                             | <b>2.3 (1.3 to 4.0)</b>                  |              |
|                                     |  |   | RTX   |                             | 1.4 (0.8 to 2.6)                         |              |
|                                     |  |   | Johnston 2013 Semin Arthr Rheum <sup>18</sup> | MarketScan (claims dataset) | ABA                                      |              |
|                                     | ADA  |   | 1.1 (0.7 to 1.7)                              |                             |  |              |
|                                     | ETA  |   | 1.3 (0.8 to 2.0)                              |                             |  |              |
|                                     | IFX  |   | 1.6 (1.0 to 2.6)                              |                             |  |              |
|                                     | Lampropoulos 2015 Clin Exp Rheumatol <sup>12</sup> | Files Laiko University Hospital                               | ADA   | IFX                         | 1.1 (p=0.819)                            | High         |
|                                     |  |   | ETA   |                             | 0.7 (p=0.559)                            |              |
|                                     | Sakai 2015 AR&T <sup>19</sup>                      | REAL  | TCZ   | TNFi                        | 2.2 (0.9 to 5.4)                         | Moderate     |
|                                     | Yun 2016 A&R <sup>20</sup>                         | Medicare claims dataset                                       | ADA   | ABA                         | 1.1 (0.9 to 1.3)                         |              |
|                                     |  |   | CZP   |                             | 1.1 (0.9 to 1.3)                         |              |
|                                     |  |   | ETA   |                             | <b>1.2 (1.1 to 1.5)</b>                  |              |
|                                     |  |   | IFX   |                             | <b>1.4 (1.2 to 1.6)</b>                  |              |
|                                     |  |   | GOL   |                             | 1.1 (0.9 to 1.4)                         |              |
|                                     |  |   | RTX   |                             | <b>1.4 (1.2 to 1.5)</b>                  |              |
|                                     | TCZ  |   | 1.1 (0.9 to 1.3)                              |                             |  |              |
| Herpes zoster                       |  |   |   |                             |  |              |
| 2013–2016                           | Pappas 2015 AC&R <sup>21</sup>                     | CORRONA   | Non-TNFi                                      | TNFi                        | 0.8 (0.5 to 1.4)                         | Low          |
| Tuberculosis                        |  |   |   |                             |  |              |
| 2013–2016                           | Chiang 2014 Comp methods <sup>16</sup>             | Taiwan's National Health Insurance Research Database          | ETA   | ADA                         | 2.4 (0.3 to 19.0)                        | High         |
|                                     | Chiu 2014 Int J Rheum Dis <sup>11</sup>            |   | ADA   | ETA                         | <b>2.4 (1.3 to 4.2)</b>                  | High         |
| Non-viral opportunistic infections† |  |   |   |                             |  |              |
| 2013–2016                           | Baddley 2014 ARD <sup>23</sup>                     | 4 US insurance datasets (SABER study (claims dataset))        | ADA   | ETA                         | 1.8 (0.8 to 4.0)                         | Moderate     |
|                                     |  |   | IFX   |                             | <b>2.9 (1.5 to 5.4)</b>                  |              |

Estimates in bold reflect a risk/ratio statistically significantly different from 1, ie association is statistically significant.

More details are found in online supplementary tables S1–S31.

\*Unadjusted estimate; no adjusted estimate reported.

†No upper border of CI given.

‡Non-viral opportunistic infections included fungal infections, tuberculosis, pneumocystosis, nocardiosis/actinomycosis, non-tuberculous mycobacteria, salmonellosis, listeriosis and legionellosis.

ABA, abatacept; ADA, adalimumab; aHR, adjusted adjusted Hazard Ratio; CORRONA, Consortium of Rheumatology Researchers of North America; CZP, certolizumab pegol; ETA, etanercept; GOL, golimumab; IFX, infliximab; REAL, Registry of Japanese Rheumatoid Arthritis Patients for Long-term Safety; RTX, rituximab; TCZ, tocilizumab; TNFi, tumour necrosis factor  $\alpha$  inhibitor.

for good quality safety studies addressing the remaining DMARDs. Only one study included a comparison between csDMARDs and the focus of that study was still on bDMARDs.<sup>9</sup> Among the studies on bDMARDs, none of them included patients on biosimilars (yet). In addition, observational studies addressing tsDMARDs (Jak inhibitor(s)) have not yet been found. However, RCT data point towards a higher risk of serious infections, infections caused by herpes zoster and tuberculosis, risks that should not be ignored and that warrant further research.<sup>2–60</sup> Finally, while glucocorticoids are gaining importance as bridging treatment for RA, no single study meeting the eligibility criteria could be found. Nevertheless, concerns regarding the long-term safety of glucocorticoids remain,<sup>2</sup> and recent studies, even though some of them are uncontrolled or may suffer from confounding by indication, point towards a higher cardiovascular risk, a higher risk of infections and higher mortality in patients taking

glucocorticoids.<sup>28 61–64</sup> These are all questions that should be addressed, likely in registries, and with the use of analytical techniques that have previously been used with success in safety studies with bDMARDs.

In line with the frequent updates of the EULAR recommendations for the management of RA, it is to expect that an update of this SLR will soon deserve careful attention, particularly if the above-mentioned unmet needs are fulfilled and more good quality safety registry data, and covering more interventions, become available. An example is the recent study from Strangfeld *et al*<sup>65</sup> showing a higher risk of lower intestinal perforation in patients taking tocilizumab compared with patients on csDMARDs, which has no longer been included in this SLR because it was accepted for publication after the update of the search for this SLR and when the task force meeting for the EULAR recommendations on the management of RA had already taken place. This and other

**Table 3** Malignancies in patients on bDMARDs compared with patients on csDMARDs or general population (observational studies)

| Year of publication             | Study ID  | Registry  | Intervention | Control csDMARDs | Control general population | aHR (intervention vs comparator/control)  | aHR (intervention vs general population)                                       | Risk of bias |
|---------------------------------|---|---|--------------|------------------|----------------------------|---|--|--------------|
| All types of cancer             |   |   |              |                  |                            |   |  |              |
| ≤2013                           | Asklings 2009 A&R <sup>51</sup>                     | ARTIS   | 3 TNFi       | csDMARDs         | General population         | TNFi vs pts starting MTX: 1.0 (0.8 to 1.2); TNFi vs csDMARDs combination therapy 1.0 (0.7 to 1.4) | 1.1 (1.0 to 1.3)   | Low          |
|                                 | Carmona 2011 Semin Arthritis Rheum <sup>52</sup>    | BIODASER  | 3 TNFi       | csDMARDs         | General population         | 0.5 (0.1 to 2.5)  | 0.7 (0.5 to 0.9)   | Low          |
|                                 | Hayes 2013 A&R <sup>53</sup>                        | Claim database  | 3 TNFi       | csDMARDs         | NR                         | 0.8 (0.6 to 1.1)<br>Ever-analysis 0.9 (0.8 to 1.1)  | NR   | Moderate     |
|                                 | Pallavicini 2010 Autoimmunity Reviews <sup>54</sup> | LORHEN  | 3 TNFi       | NR               | General population         | NR  | Milan*: 0.9 (0.6 to 1.5) to Varese 1.1 (0.6 to 1.7)                            | Moderate     |
|                                 | Strangfeld 2010 AR&T <sup>55</sup>                  | RABBIT  | 3 TNFi       | csDMARDs         | General population         | 0.7 (0.4 to 1.1)<br>1.4 (0.6 to 3.5)  | 0.8 (0.5 to 1.0)<br>NR   | Low          |
| 2013–2016                       | Berghen 2015 Clin Rheumatol <sup>25</sup>           | Cases from the Leuven University Hospital                     | 3 TNFi       | NR               | General population         | NR  | ♂163.5 (156.8 to 170.6)† ♀145.5 (137.2 to 154.3)                               | Moderate     |
|                                 | Aaltonen 2015 J Rheum <sup>10</sup>                 | National Register for Biologic Treatment in Finland (ROB-FIN) | 3 TNFi       | csDMARDs         | NR                         | 1.2 (0.6 to 2.2)<br>1.1 (0.5 to 2.2)<br>1.3 (0.7 to 2.6)<br>1.2 (0.4 to 3.1)<br>1.2 (0.5 to 3.2)  | NR   | Low          |
|                                 | Morgan 2014 Rheumatology <sup>14</sup>              | BSRBR   | ETA          | csDMARDs         | NR                         | 0.8 (0.7 to 1.0)  | NR   | Low          |
|                                 | Solomon 2014 Semin Arthr Rheum <sup>9</sup>         | CORRONA   | 3 TNFi       | MTX              | NR                         | 0.3 (0.1 to 0.6)<br>0.4 (0.1 to 2.6)<br>1.6 (0.4 to 6.0)  | NR   | Low          |
|                                 |   |   | RTX          |                  |                            |   |  |              |
|                                 |   |   | ABA          |                  |                            |   |  |              |
| Patients with history of cancer |   |   |              |                  |                            |   |  |              |
| ≤2013                           | Dixon 2010 AC&R <sup>68</sup>                       | BSRBR   | 3 TNFi       | csDMARDs         | NR                         | 0.5 (0.1 to 2.2); censoring after first cancer 0.5 (0.1 to 2.2)                                   | NR   | Low          |
| Solid cancers                   |   |   |              |                  |                            |   |  |              |
| 2013–2016                       | Mercer 2015 ARD <sup>26</sup>                       | BSRBR   | 3 TNFi       | csDMARDs         | NR                         | 0.8 (0.6 to 1.1)<br>0.8 (0.6 to 1.1)<br>0.9 (0.7 to 1.2)<br>0.8 (0.6 to 1.1)                      | NR   | Low          |
|                                 |   |   | ADA          |                  |                            |   |  |              |
|                                 |   |   | ETA          |                  |                            |   |  |              |
|                                 |   |   | IFX          |                  |                            |   |  |              |
|                                 | Solomon 2014 Semin Arthr Rheum <sup>9</sup>         | CORRONA   | 3 TNFi       | MTX              | NR                         | 0.2 (0.1 to 0.6)<br>0.3 (0.0 to 3.4)<br>0.4 (0.1 to 2.2)  | NR   | Low          |
|                                 |   |   | RTX          |                  |                            |   |  |              |
|                                 |   |   | ABA          |                  |                            |   |  |              |
| Lymphoma                        |   |   |              |                  |                            |   |  |              |
| ≤2013                           | Asklings 2009 ARD <sup>69</sup>                     | ARTIS   | 3 TNFi       | csDMARDs         | Gen population             | 1.4 (0.8 to 2.1)  | 2.7 (1.8 to 4.1)   | Low          |
|                                 | Mariette 2010 ARD <sup>70</sup>                     | RATIO   | 3 TNFi       | NR               | Gen population             | NR  | 2.3 (1.6 to 3.3)   | Low          |
|                                 | Carmona 2011 Semin Arthritis Rheum <sup>52</sup>    | BIODASER  | 3 TNFi       | csDMARDs         | General population         | NR  | Hodgkin's lymphoma 5.3 (0.1 to 29.5); non-Hodgkin's lymphoma 1.5 (0.31 to 4.4) | Low          |

Continued

Table 3 Continued

| Year of publication      | Study ID  | Registry                                  | Intervention         | Control csDMARDs | Control general population | aHR (intervention vs comparator/control)  | aHR (intervention vs general population)             | Risk of bias |
|--------------------------|---|---|----------------------|------------------|----------------------------|---|--|--------------|
| 2013–2016                | Haynes 2013 A&R <sup>53</sup>                       | Claim database                            | 3 TNFi               | csDMARDs         | NR                         | 0.8 (0.3 to 2.1)<br>Ever-analysis 1.3 (0.7 to 2.2)  | NR   | Moderate     |
|                          | Pallavicini 2010 Autoimmunity Reviews <sup>54</sup> | LOHREN                                    | 3 TNFi               | NR               | General population         | NR  | Milan 6.0 (1.6 to 15.4) to Varese 5.0 (1.3 to 12.7); | Moderate     |
|                          | Berghen 2015 Clin Rheumatol <sup>25</sup>           | Cases from the Leuven University Hospital | 3 TNFi               | NR               | General population         | NR  | ♂ 423.6 (361.9–492.8)†<br>♀ 1135 (1003.1–1279.5)     | Moderate     |
| Non-melanoma skin cancer |   |   |                      |                  |                            |   |  |              |
| ≤2013                    | Amari 2011 Rheumatology <sup>71</sup>               | Claim database                            | 3 TNFi               | csDMARDs         | NR                         | 1.4 (1.2 to 1.6);<br>TNFi vs MTX 1.4 (1.2 to 1.7)   | NR   | Moderate     |
|                          | Mercer 2012 ARD <sup>72</sup>                       | BSRBR                                     | 3 TNFi               | csDMARDs         | General population         | BCC 1.0 (0.5 to 1.7), SCC 1.2 (0.4 to 3.8); first cancer per subject BCC 0.8 (0.5 to 1.5) | 1.7 (1.4 to 2.0)                                     | Low          |
|                          | Haynes 2013 A&R <sup>53</sup>                       | Claim database                            | 3 TNFi               | csDMARDs         | NR                         | 0.8 (0.5 to 1.4)<br>Ever-analysis 1.1 (0.8 to 1.5)  | NR   | Moderate     |
| 2013–2016                | Solomon 2014 Semin Arthr Rheum <sup>9</sup>         | CORRONA                                   | 3 TNFi<br>RTX<br>ABA | MTX              | NR                         | 0.4 (0.1 to 1.2)<br>0.7 (0.0 to 13.6)<br>15.3 (2.1 to 114.0)†                             | NR   | Low          |
| Melanoma                 |   |   |                      |                  |                            |   |  |              |
| ≤2013                    | Raaschou 2013 BMJ <sup>56</sup>                     | ARTIS                                     | 5 TNFi               | csDMARDs         | NR                         | 1.5 (1.0 to 2.2)  | NR   | Low          |

Estimates in bold reflect a risk/ratio statistically significantly different from 1, ie association is statistically significant.

More details are found in online supplementary tables S32–S38.

\*Milan refers the Milan Cancer Report and Varese to the Varese Cancer Registry database. These were the general population comparators used.

†Standardised incidence rates are reported, with the general population as the reference; SIR of 100 means no difference between incidence rates.

‡n=2 cases.

ABA, abatacept; ADA, adalimumab; aHR, adjusted HR; ANA, anakinra; ARTIS, Swedish Biologics Register; BCC, basal cell carcinoma; bDMARDs, biological disease-modifying antirheumatic drugs; BSRBR, British Society of Rheumatology Biologics Register; CORRONA, Consortium of Rheumatology Researchers of North America; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; ETA, etanercept; IFX, infliximab; LOHREN, Lombardy Rheumatology Network (Italian Biologics Register); MTX, methotrexate; NA, not available (not mentioned in the original article); NR, not reported; pts, patients; RABBIT, Rheumatoid Arthritis Observation of Biologic Therapy (in German); RATIO, French Biologics Register; RTX, rituximab; SCC, squamous cell carcinoma; TNFi, tumour necrosis factor  $\alpha$  inhibitor.

relevant studies should be considered in a future update of this SLR.

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