Short report

How do we use biologics in rheumatoid arthritis patients with a history of malignancy? An assessment of treatment patterns using Scandinavian registers

Katerina Chatzidionysiou,1 Bénédicte Delcoigne,1 Thomas Frisell,1 Merete L Hetland,2,3 Bente Glintborg,2,3 Iene dreyer,4,5 René Cordtz,6 Kristian Zobbe,6 Dan Nordström,7 Nina Trokovic,7 Kalle Aaltonen,8 Sella Aarrestad Provan,9 Gerdur Grondal,10 Bjorn Gudbjornsson,11 Johan Askling1

Immune competence is of importance for the occurrence and outcome of malignancies, as exemplified by the effects of immune checkpoint inhibitors in the treatment of malignancies.1 An increased risk for malignancies has been one of the main concerns since the introduction of biological disease-modifying anti-rheumatic drugs (bDMARDs) for the treatment of chronic inflammatory arthritis. Most treatment guidelines have therefore issued caution against using bDMARDs (tumour necrosis factor inhibitors (TNFi) in particular) in patients with a history of cancer within 5–10 years. So far, most (though not all) studies of cancer incidence following treatment with TNFi and other bDMARDs, and of recurrence of pretreatment cancers following treatment with TNFi, have been reassuring.2–9 The 2015 ACR recommendations for treatment of rheumatoid arthritis (RA) recommend that patients with a history of previous solid organ malignancy should be treated as patients without this condition, although the level of evidence is low.10

What is already known about this subject?
► According to RA treatment recommendations, patients with a history of previous solid organ malignancy should be treated as patients without this condition, although the level of evidence is low.

What does this study add?
► This large multinational register-based study quantified the proportion of RA patients starting a bDMARD who had a prior malignancy (1–6%). This proportion was significantly higher for rituximab (8–17%), demonstrating a preference for rituximab in this patient population.

How might this impact on clinical practice?
► There is a reluctance to use bDMARDs and especially TNF inhibitors in RA patients with a history of malignancy, which might imply a risk for undertreatment of some patients. This underscores the need for more data.

The aim of the present study was to assess the relative use of different bDMARDs in patients with RA and history of cancer. We used real-life data from the DANBIO (Denmark), ROB-FIN (Finland), NOR-DMARD (Norway) and ARTIS (Sweden) bDMARD registries. We identified patients with RA who initiated any bDMARD between year 2010–2017, regardless of type or number of prior bDMARDs. We identified patients with a clinical rheumatologist-assigned diagnosis of RA regardless of fulfilment of exact classification criteria. We identified the subgroup of patients with prior malignancy 10-year prior to starting the bDMARD in question through linkage to national cancer registers. Any malignancy (invasive or in situ) apart from benign tumours was defined as malignancy. Patients could contribute more than one treatment course. Both non-melanoma and melanoma skin cancer were included. The frequency of RA patients with a history of malignancy (according to the definition initiated any bDMARD between year 2010–2017, regardless of type or number of prior bDMARDs. We identified patients with a clinical rheumatologist-assigned diagnosis of RA regardless of fulfilment of exact classification criteria. We identified the subgroup of patients with prior malignancy 10-year prior to starting the bDMARD in question through linkage to national cancer registers. Any malignancy (invasive or in situ) apart from benign tumours was defined as malignancy. Patients could contribute more than one treatment course. Both non-melanoma and melanoma skin cancer were included. The frequency of RA patients with a history of malignancy (according to the definition
Table 1  Number and characteristics of patients with RA starting a bDMARD, a TNF inhibitor or a non-TNF inhibitor, during 2010–2017, as well as number of those patients with a previous history of cancer 10-year prior to starting the bDMARD in question, distinguishing invasive and in situ cancer, across different bDMARDs. Data from four large Scandinavian biologics registers. Information when the number of patient was less than 5 is not presented.

| Patients (n) | TNF inhibitors | Non-TNF inhibitors |
|--------------|----------------|--------------------|
|              | Adalimumab     | Certolizumab pegol | Etanercept | Golimumab | Infliximab | Abatacept | Rituximab | Tocilizumab |
| Denmark      | 1212           | 1444               | 2816       | 434       | 1528       | 1109      | 984       | 1703       |
| Finland      | 666            | 428                | 1018       | 517       | 241        | 544       | 910       | 442        |
| Norway       | 102            | 460                | 468        | 150       | 208        | 92        | 223       | 173        |
| Sweden       | 2984           | 2012               | 6529       | 1861      | 2714       | 2701      | 3488      | 2477       |
| TOTAL        | 4864           | 4344               | 10831      | 2962      | 4691       | 4446      | 5605      | 4795       |

Any history of cancer

| Patients (n) | TNF inhibitors | Non-TNF inhibitors |
|--------------|----------------|--------------------|
|              | Adalimumab     | Certolizumab pegol | Etanercept | Golimumab | Infliximab | Abatacept | Rituximab | Tocilizumab |
| Denmark      | 16 (2.4%)      | 16 (3.7%)          | 35 (3.4%)  | 20 (3.8%) | 8 (3.3%)   | 44 (8%)   | 118 (13%) | 31 (7%)    |
| Finland      | 2 (2.0%)       | 7 (1.5%)           | 6 (1.3%)   | 3 (2.0%)  | 5 (2.4%)   | 1 (1.0%)  | 26 (11.7%)| 6 (3.5%)   |
| Norway       | 152 (5.1%)     | 108 (5.3%)         | 397 (6.1%) | 83 (4.5%) | 139 (5.1%) | 186 (6.9%)| 493 (14%) | 145 (5.9%) |
| Sweden       | 61/91          | 31/77              | 142/255    | 38/45     | 59/80      | 63/123    | 98/395    | 45/100     |
| ALL          | 182 (3.7%)     | 157 (3.6%)         | 491 (4.5%) | 111 (3.7%)| 179 (3.8%) | 247 (5.6%)| 806 (14.4%)| 218 (4.5%) |

Time (years) since cancer*, median (IQR)

| Patients (n) | TNF inhibitors | Non-TNF inhibitors |
|--------------|----------------|--------------------|
|              | Adalimumab     | Certolizumab pegol | Etanercept | Golimumab | Infliximab | Abatacept | Rituximab | Tocilizumab |
| Denmark      | 4 (2–5)        | 7 (2–7)            | 3 (2–6)    | 4 (4–7)   | 5 (2–7)    | 4 (2–7)   | 3 (1–6)   | 6 (3–8)    |
| Finland      | 5 (4–6)        | 4 (2–5)            | 4 (2–6)    | 3 (1–6)   | 3 (2–6)    | 3 (4–6)   | 3 (2–6)   | 3 (1–5)    |
| Norway       | <5 patients    | 7 (5–8)            | 6 (3–9)    | <5 patients| 5 (2–9)    | <5 patients| 2 (2–5)   | 6 (2–8)    |
| Sweden       | 4 (2–6)        | 4 (2–7)            | 4 (2–7)    | 4 (2–7)   | 4 (2–7)    | 4 (2–6)   | 3 (1–6)   | 4 (2–7)    |

Median (IQR) age at bDMARD start, years

| Patients (n) | TNF inhibitors | Non-TNF inhibitors |
|--------------|----------------|--------------------|
|              | Adalimumab     | Certolizumab pegol | Etanercept | Golimumab | Infliximab | Abatacept | Rituximab | Tocilizumab |
| Denmark      | 56 (46–65)     | 57 (48–66)         | 59 (50–68) | 56 (45–66)| 60 (49–69)| 59 (50–68)| 61 (52–70)| 59 (50–69) |
| History of cancer | 63 (55–70) | 52 (41–67) | 60 (47–73) | 60 (60–70)| 60 (47–73)| 63 (47–71)| 66 (58–73)| 61 (43–71) |
| Finland      | 51 (43–61)     | 53 (44–62)         | 52 (41–63)| 52 (43–62)| 48 (37–59)| 56 (48–65)| 63 (56–71)| 54 (51–61) |
| History of cancer | 62 (56–70) | 63 (55–69) | 66 (59–70)| 67 (60–69)| 59 (54–62)| 65 (61–72)| 68 (61–75)| 66 (57–72) |
| Norway       | 52 (50–54)     | 54 (53–55)         | 53 (52–53)| 52 (50–53)| 55 (53–56)| 54 (53–56)| 58 (56–59)| 54 (53–55) |
| History of cancer | <5 patients | 64 (60–75) | 63 (57–75)| <5 patients| <5 patients| <5 patients| <5 patients| 63 (58–69) |
|              | 52 (50–54)     | 54 (53–55)         | 53 (52–53)| 52 (50–53)| 55 (53–56)| 54 (53–56)| 58 (56–59)| 54 (53–55) |

Continued
| Patients (n) | TNF inhibitors | Non-TNF inhibitors |
|-------------|----------------|------------------|
|             | Adalimumab     | Certolizumab pegol | Etanercept | Golimumab | Infliximab | Abatacept | Rituximab | Tocilizumab |
| Sweden      |                |                  |             |           |            |           |           |             |
| All         | 58 (46–67)     | 58 (47–67)       | 58 (46–67) | 58 (46–66) | 59 (48–67) | 61 (51–69) | 64 (54–72) | 59 (48–67) |
| History of cancer | 67 (57–72) | 67 (52–74) | 67 (56–73) | 65 (50–71) | 65 (55–73) | 69 (61–75) | 68 (61–74) | 65 (58–73) |
| Female, %   |                |                  |             |           |            |           |           |             |
| Denmark     |                |                  |             |           |            |           |           |             |
| All         | 78%            | 75%              | 77%         | 74%       | 75%        | 79%       | 78%       | 77%        |
| History of cancer | 83%     | 85%              | 85%         | <5 patients | 74%        | 75%       | 77%       | 78%        |
| Finland     |                |                  |             |           |            |           |           |             |
| All         | 73%            | 75%              | 78%         | 76%       | 70%        | 84%       | 74%       | 78%        |
| History of cancer | 69%     | 88%              | 86%         | 80%       | 100%       | 91%       | 76%       | 71%        |
| Norway      |                |                  |             |           |            |           |           |             |
| All         | 85%            | 75%              | 76%         | 77%       | 73%        | 84%       | 77%       | 84%        |
| History of cancer | <5 patients | 71%              | 100%        | <5 patients | <5 patients | <5 patients | <5 patients | 64%        | 71%        |
| Sweden      |                |                  |             |           |            |           |           |             |
| All         | 76%            | 76%              | 77%         | 78%       | 74%        | 81%       | 76%       | 80%        |
| History of cancer | 79%     | 77%              | 78%         | 78%       | 72%        | 82%       | 71%       | 77%        |
| Prior bDMARDs (n; median, IQR) | | | | | | | | |
| Denmark     |                |                  |             |           |            |           |           |             |
| All         | 1 (0–2)        | 1 (0–2)          | 1 (0–2)     | 1 (0–2)   | 1 (0–2)    | 0 (0–2)   | 0 (0–2)   | 1 (0–2)    |
| History of cancer | 0 (0–0) | 0 (0–0)          | 0 (0–0)     | 0 (0–1)   | 0 (0–1)    | 0 (0–0)   | 0 (0–0)   | 0 (0–0)    |
| Finland     |                |                  |             |           |            |           |           |             |
| All         | 0 (0–1)        | 1 (0–2)          | 0 (0–0)     | 0 (0–1)   | 0 (0–1)    | 1 (0–2)   | 0 (0–2)   | 2 (1–3)    |
| History of cancer | 0 (0–1) | 2 (1–4)          | 0 (0–1)     | 1 (0–3)   | 0 (0–2)    | 1 (0–2)   | 0 (0–1)   | 1 (0–3)    |
| Norway      |                |                  |             |           |            |           |           |             |
| All         | 1 (0–1)        | 0 (0–1)          | 0 (0–1)     | 0 (0–1)   | 0 (0–1)    | 3 (2–4)   | 2 (1–2)   | 2 (1–3)    |
| History of cancer | <5 patients | 0 (0–0)          | 1 (0–2)     | <5 patients | <5 patients | <5 patients | <5 patients | 0 (0–1)    | 3 (1–3)    |
| Sweden      |                |                  |             |           |            |           |           |             |
| All         | 1 (0–1)        | 0 (0–2)          | 0 (0–1)     | 1 (0–1)   | 0 (0–1)    | 2 (1–3)   | 1 (0–2)   | 2 (1–3)    |
| History of cancer | 1 (0–2) | 0 (0–2)          | 0 (0–1)     | 1 (0–2)   | 0 (0–1)    | 1 (1–3)   | 1 (0–2)   | 2 (1–3)    |

*Time from cancer diagnosis was defined as the time from first diagnosis of cancer until the start of the bDMARD.

TNF, tumor necrosis factor; IQR, interquartile range; bDMARD, biologic disease-modifying anti-rheumatic drug; N/A, non-available.
above) in each bDMARD group, as well as basic demographic and disease characteristics (age, gender, number of prior bDMARDs, years from cancer diagnosis until start of the bDMARD) was assessed across the different bDMARD groups. Switches from bio-original to biosimilar were regarded as one treatment.

A total of 42 638 RA patients initiating a bDMARD treatment were included (table 1). Initiators of non-TNFi biologics were generally older than TNFi initiators, with the highest age at start for rituximab, especially in Sweden and Finland (table 1). Overall, among the bDMARD initiators in Denmark, Finland, Norway and Sweden, 344/11 230=3%, 288/4766=6%, 56/1876=3% and 1703/24 766=6.9%, respectively, had prior cancer. Whereas there was little variation across individual TNFi inhibitors ranging from 1% to 6%, the proportion of patients with a history of cancer at treatment start was higher among patients on non-anti-TNF bDMARDs, especially for rituximab (8–17%). The median time (years) since the cancer diagnosis ranged from 2 to 7 years, with a tendency towards a shorter time for rituximab (table 1).

As expected, we noted that the proportion of patients starting a bDMARD during the period 2010–2017 with a prior malignancy was low. Among these initiators, however, there was a clear preference for non-TNFi, in particular rituximab. The latter could in part be explained by differences in age at treatment start, as patients on rituximab tend to be older compared with patients on other bDMARDs. However, the small differences in median age among patients with history of cancer across the bDMARD groups under study supports the hypothesis that there is a preference for rituximab by clinicians for treatment of patients with history of cancer. Rituximab is being used for several haematological malignancies, which might at least partly explain the preference, although the underlying evidence for this preference in other types of cancers remains incomplete. Another interesting observation was that the proportion of female patients with a history of cancer was somewhat higher compared with patients with no history of cancer in the TNFi groups, but not in the non-TNFi group. A possible explanation for this could be the different choice of bDMARD in different types of cancer. Finally, there is heterogeneity not only in treatment channelling, but also due to different prescription patterns across countries.

Our results underscore both the reluctance to use bDMARDs and especially TNFi in RA patients with a history of malignancy, which implies a risk for undertreatment of some patients, and the need for more data on the benefit–risk ratio in this treatment context.

Acknowledgements We thank all the departments contributing to the clinical data collection in the participating biologic registers.

Contributors All authors contributed to study design. KC, BC and RC performed the analysis of raw data. All authors contributed to the interpretation of the results and in the preparation of the manuscript.

Funding This study was partly funded by grants from Nord-Forsk and FORUM. Competing interests KC: received consultancy fees from Eli Lilly, AbbVie and Pfizer. MLH: received grant/research support from BMS, MSD, AbbVie, Roche, Novartis, Biogen and Pfizer; consultancy fees from Eli Lilly; speaker’s fees from Orion Pharma, Biogen, Pfizer, CellTrion, Merck and Samsung Bioepis. BG: Pfizer, Biogen, BMS (research grants). LD: received grant/research support from BMS; consultancy fees from Janssen pharmaceuticals; speaker’s fees from Eli Lilly, UCB, MSD. DN: received consultancy fees from AbbVie, BMS, Celgene, MSD, Novartis, Pfizer, Roche and UCB. SAP: speaker and consultancy fees from Novartis. BJG: received speaker fees from Novartis. JA: Karolinska Institutet has entered into agreements between Karolinska Institutet (JA as principal investigator) with the following companies mainly regarding the safety monitoring of b/ts DMARDs in rheumatology: AbbVie, BMS, MSD, Eli Lilly, Pfizer, Roche, Samsung Bioepis, Sanoﬁ and UCB. BD, TF, RC, KZ, NT, KA, GG: None.

Patient consent for publication Patients were involved in the design, conduct, reporting or dissemination plans of this research. Patient partners have been active members of the Nordforsk collaboration and they have been involved from the initial stages of this research project, participating in the forming of the research question, study design, interpretation and signiﬁcance of the results.

Ethics approval The appropriate ethical committees and/or data protection committees in each country approved the study (approval codes for Sweden: 2015/1844-31/2; Denmark: RH-2015–209, I-suite 04145; Norway: 2011/1339 and 2017/243; Finland: 73/13/03/00/2014). Individual patient consent was not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All relevant data are included in the article or uploaded as supplementary information.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs Katerina Chatzidionysiou http://orcid.org/0000-0002-2669-1247
Bente Glintborg http://orcid.org/0000-0002-9391-8482
Sella Aarestad Provan http://orcid.org/0000-0001-5442-902X

REFERENCES

1 Farkona S, Diamandis EP, Blasutig IM. Cancer immunotherapy: the beginning of the end of cancer? *BMJ* 2016;14:73.

2 Raaschou P, Simard JF, Holmqvist M, et al. Rheumatoid arthritis, anti-tumour necrosis factor therapy, and risk of malignant melanoma: nationwide population based prospective cohort study from Sweden. *BMJ* 2013;346:f1939.
3 Raaschou P, Simard JF, Hagelberg CA, et al. Rheumatoid arthritis, anti-tumour necrosis factor treatment, and risk of squamous cell and basal cell skin cancer: cohort study based on nationwide prospectively recorded data from Sweden. BMJ 2016;352:i262.

4 Wolfe F, Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: analyses from a large US observational study. Arthritis Rheum 2007;56:2886–95.

5 Askling J, Fahrbach K, Nordstrom B, et al. Cancer risk with tumor necrosis factor alpha (TNF) inhibitors: meta-analysis of randomized controlled trials of adalimumab, etanercept, and infliximab using patient level data. Pharmacoepidemiol Drug Saf 2011;20:119–30.

6 Wadström H, Frisell T, Askling J. Malignant neoplasms in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors, tocilizumab, abatacept, or rituximab in clinical practice: a nationwide cohort study from Sweden. JAMA 2017;177:1605–12.

7 Mercer LK, Askling J, Raaschou P, et al. Risk of invasive melanoma in patients with rheumatoid arthritis treated with biologics: results from a collaborative project of 11 European biologic registers. Ann Rheum Dis 2017;76:386–91.

8 Dreyer L, Mellemkjær L, Andersen AR, et al. Incidences of overall and site specific cancers in TNFα inhibitor treated patients with rheumatoid arthritis and other arthritis—a follow-up study from the DANBIO registry. Ann Rheum Dis 2013;72:79–82.

9 Dreyer L, Cordtz RL, Hansen IMJ, et al. Risk of second malignant neoplasm and mortality in patients with rheumatoid arthritis treated with biological DMARDs: a Danish population-based cohort study. Ann Rheum Dis 2018;77:510–4.

10 Singh JA, Saag KG, Bridges SL, et al. 2015 American college of rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken) 2016;68:1–28.

11 Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American college of rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res 2012;64:625–39.