




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 Glinthorg ^{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

To cite: Chatzidionysiou K, Delcoigne B, Frisell T, *et al.* How do we use biologics in rheumatoid arthritis patients with a history of malignancy? An assessment of treatment patterns using Scandinavian registers. *RMD Open* 2020;**6**: e001363. doi:10.1136/rmdopen-2020-001363

Received 16 June 2020
Revised 18 August 2020
Accepted 18 August 2020

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 pre-treatment 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,¹⁰ though acknowledging the low level of evidence, whereas previous recommendations suggested rituximab.¹¹ Similarly, there is no consensus regarding the time period from cancer diagnosis until the safe initiation of a bDMARD. Thus, scientific evidence supporting clinical decision-making in this context is scarce.

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 registers. We identified patients with RA who

Key messages

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.

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



© Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Katerina Chatzidionysiou;
aikaterini.chatzidionysiou@ki.se

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	4964	4344	10 831	2962	4691	4446	5605	4795
Any history of cancer	Adalimumab	Certolizumab pegol	Etanercept	Golimumab	Infliximab	Abatacept	Rituximab	Tocilizumab
Denmark								
N (%) patients with history of cancer	12 (1%)	26 (1.8%)	53 (1.9%)	5 (1.2%)	27 (1.8%)	16 (1.4%)	169 (17.2%)	36 (2.1%)
N patients with in situ/invasive cancer	5/7	17/9	22/31	<5/<5	11/16	6/10	17/152	18/18
Finland								
N (%) of patients with any history of cancer	16 (2.4%)	16 (3.7%)	35 (3.4%)	20 (3.8%)	8 (3.3%)	44 (8%)	118 (13%)	31 (7%)
N. patients with in situ/invasive cancer	1/15	2/14	2/33	2/18	3/5	5/39	3/115	2/28
Norway								
N (%) of patients with any history of cancer	2 (2.0%)	7 (1.5%)	6 (1.3%)	3 (2.0%)	5 (2.4%)	1 (1.0%)	26 (11.7%)	6 (3.5%)
N. patients with in situ/invasive cancer	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Sweden								
N (%) patients with any history of cancer	152 (5.1%)	108 (5.3%)	397 (6.1%)	83 (4.5%)	139 (5.1%)	186 (6.9%)	493 (14%)	145 (5.9%)
N. patients with in situ/invasive cancer	61/91	31/77	142/255	38/45	59/80	63/123	98/395	45/100
ALL								
N (%) patients with any history of cancer	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)	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	Adalimumab	Certolizumab pegol	Etanercept	Golimumab	Infliximab	Abatacept	Rituximab	Tocilizumab
Denmark								
▲ All	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								
▲ All	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								
▲ All	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	63 (58–69)	67 (52–68)

Continued

Table 1 Continued

Patients (n)	TNF inhibitors					Non-TNF inhibitors				
	Adalimumab	Certolizumab pegol	Etanercept	Golimumab	Infliximab	Abatacept	Rituximab	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)	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)	69 (61–75)	68 (61–74)	65 (58–73)
Female, %										
Denmark										
▲ All	78%	75%	77%	74%	75%	79%	78%	79%	78%	77%
▲ History of cancer	83%	85%	85%	<5 patients	74%	75%	77%	75%	77%	78%
Finland										
▲ All	73%	75%	78%	76%	70%	84%	74%	84%	74%	78%
▲ History of cancer	69%	88%	86%	80%	100%	91%	76%	91%	76%	71%
Norway										
▲ All	85%	75%	76%	77%	73%	84%	77%	84%	77%	84%
▲ History of cancer	<5 patients	71%	100%	<5 patients	<5 patients	<5 patients	64%	<5 patients	64%	71%
Sweden										
▲ All	76%	76%	77%	78%	74%	81%	76%	81%	76%	80%
▲ History of cancer	79%	77%	78%	78%	72%	82%	71%	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)	1 (0–2)	0 (0–2)	1 (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)	0 (0–0)	0 (0–0)
Finland										
▲ All	0 (0–1)	1 (0–2)	0 (0–1)	0 (0–2)	0 (0–1)	1 (0–2)	0 (0–2)	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 (0–2)	0 (0–1)	1 (0–3)
Norway										
▲ All	1 (0–1)	0 (0–1)	0 (0–1)	1 (0–2)	0 (0–1)	3 (2–4)	2 (1–2)	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	0 (0–1)	<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)	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)	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.

Author affiliations

¹Clinical Epidemiology Division, Department of Medicine Solna, Karolinska Institutet, Karolinska Institutet Department of Medicine Solna, Stockholm, Sweden

²DANBIO and Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Centre of Head and Orthopedics, Rigshospitalet, Copenhagen, Denmark

³Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

⁴Department of Rheumatology, Aalborg University Hospital, Aalborg, Denmark

⁵Department of Clinical Medicine, Aalborg Universitet, Aalborg, Denmark

⁶Center for Rheumatology and Spine Diseases, Rigshospitalet, Gentofte Hospital, The Parker Institute, Frederiksberg Hospital Parker Institute, Frederiksberg, Denmark

⁷Helsinki University and Hospital (ROB-FIN), Departments of Medicine and Rheumatology, Helsinki University Central Hospital, Helsinki, Finland

⁸Pharmaceuticals Pricing Board, Ministry of Social Affairs and Health, Helsinki, Finland

⁹Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway

¹⁰Department of Rheumatology and Centre for Rheumatology Research, National University Hospital of Iceland, Reykjavik, Iceland

¹¹Centre for Rheumatology Research, University Hospital, and Faculty of Medicine, University of Iceland, Reykjavik, Iceland

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 FOREUM.

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 data relevant to the study 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 Glinthorg <http://orcid.org/0000-0002-8931-8482>

Sella Aarrestad 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? *BMC Med* 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 TNF α inhibitor treated patients with rheumatoid arthritis and other arthritides—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;68:1–26.
- 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.