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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 Askling[1]

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For numbered affiliations see end of article.

Correspondence to
Katerina Chatzidionysiou; aikaterini.chatzidionysiou@ki.se

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 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

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 reluctancy 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.

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

	TNF inhibitors					Non-TNF inhibitors		
Patients (n)	**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

	TNF inhibitors					Non-TNF inhibitors		
Patients (n)	**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, %	**Adalimumab**	**Certolizumab pegol**	**Etanercept**	**Golimumab**	**Infliximab**	**Abatacept**	**Rituximab**	**Tocilizumab**
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	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)	**Adalimumab**	**Certolizumab pegol**	**Etanercept**	**Golimumab**	**Infliximab**	**Abatacept**	**Rituximab**	**Tocilizumab**
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)
► 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 (0–1)	0 (0–2)	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)	1 (0–2)	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	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.

Author affiliations
[1]Clinical Epidemiology Division, Department of Medicine Solna, Karolinska Institutet, Karolinska Institutet Department of Medicine Solna, Stockholm, Sweden
[2]DANBIO and Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Centre of Head and Orthopedics, Rigshospitalet, Copenhagen, Denmark
[3]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[4]Department of Rheumatology, Aalborg University Hospital, Aalborg, Denmark
[5]Department of Clinical Medicine, Aalborg Universitet, Aalborg, Denmark
[6]Center for Rheumatology and Spine Diseases, Rigshospitalet, Gentofte Hospital, The Parker Institute, Frederiksberg Hospital Parker Institute, Frederiksberg, Denmark
[7]Helsinki University and Hospital (ROB-FIN), Departments of Medicine and Rheumatology, Helsinki University Central Hospital, Helsinki, Finland
[8]Pharmaceuticals Pricing Board, Ministry of Social Affairs and Health, Helsinki, Finland
[9]Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway
[10]Department of Rheumatology and Centre for Rheumatology Research, National University Hospital of Iceland, Reykjavik, Iceland
[11]Centre for Rheumatology Research, University Hospital, and Faculty of Medicine, University of Iceland, Reykjavik, Iceland

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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.

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ORCID iDs
Katerina Chatzidionysiou http://orcid.org/0000-0002-2669-1247
Bente Glintborg http://orcid.org/0000-0002-8931-8482
Sella Aarrestad Provan http://orcid.org/0000-0001-5442-902X

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