Original research

Does autoimmune thyroid disease affect rheumatoid arthritis disease activity or response to methotrexate?

Kristin Waldenlind, Bénédicte Delcoigne, Saedis Saevarsdottir, Johan Askling

ABSTRACT

Objective To investigate if autoimmune thyroid disease (AITD) impacts rheumatoid arthritis (RA) disease activity or response to methotrexate.

Methods A nationwide register-based cohort study of 9044 patients with new-onset RA from the Swedish Rheumatology Quality Register year 2006–2016, with linkage to other nationwide registers to identify comorbidity with AITD defined as thyroxine prescription before RA diagnosis, excluding non-autoimmune causes. We compared RA disease activity using 28-joint Disease Activity Score (DAS28) and its components, and EULAR response, between patients with and without AITD, using logistic regression.

Results At diagnosis, patient reported outcome measures (PROMs; patient global, Health Assessment Questionnaire Disability Index and pain) but not objective disease activity measures (erythrocyte sedimentation rate and swollen joint count) were significantly higher (p<0.05 for all PROMs) among RA patients with AITD compared with those without. The level of DAS28 was 5.2 vs 5.1. By contrast, AITD had little influence on EULAR response to methotrexate at 3 months (OR of non/moderate response=0.95, 95% CI 0.8 to 1.1), nor at 6 months. When stratified by age, however, AITD was more common among EULAR non/moderate responders at 3 and 6 months in patients below 45 years resulting in ORs of non/moderate response of 1.44 (0.76–2.76) and 2.75 (1.04–7.28).

Conclusion At diagnosis, RA patients with concomitant AITD score worse on patient reported but not on objective RA disease activity measures, while DAS28 was only marginally elevated. The overall chance of achieving a EULAR good response at 3 or 6 months remains unaffected, although among a limited subgroup of younger patients, AITD may be a predictor for an inferior primary response.

INTRODUCTION

Autoimmune thyroid disease (AITD), including hypothyroidism and hyperthyroidism of autoimmune origin, is the most common autoimmune disease in the general population, with a prevalence of approximately 5%. The prevalence of AITD is increased in patients with rheumatoid arthritis (RA), making AITD one of the most common comorbid conditions in RA. The underlying pathogenic mechanisms of the co-occurrence between AITD and RA are not well understood, but polymorphisms in genes involved in the regulation of T-cell response may play a key role.

Key messages

What is already known about this subject?

- Autoimmune thyroid disease (AITD) increases the risk of RA. With a prevalence of approximately 10%, AITD is also one of the most common comorbid conditions in patients with RA. Yet, it is less well understood whether AITD affects also the RA phenotype and response to anti-rheumatic therapies.

What does this study add?

- In this Swedish cohort study of early RA patients, the disease activity and treatment response to methotrexate as first-line therapy was compared between patients with early RA and AITD vs RA patients without this comorbidity.

- AITD, present among 11% of all the patients with RA, was linked to worse subjective but not to worse objective measures of RA disease activity. However, AITD did not impact response to treatment, with one exception, young patients with both RA and AITD, who were less likely to achieve a good response to methotrexate.

How might this impact on clinical practice?

- Through worse subjective RA disease activity components, concomitant AITD influences the phenotypic presentation of RA and the observed composite treatment response measures used in clinical practice.

- When treating and evaluating early RA patients with concomitant AITD, it is of importance to pay attention not only to the overall disease activity and response measures such as DAS28, but to unpick its components.
In contrast to the well-established increased occurrence of RA in patients with AITD and increased occurrence of AITD in patients with RA, considerably less is known about the impact of AITD on the phenotypic presentation of RA, and on its impact on response to anti-rheumatic therapies. Previous findings indicate an association between hypothyroidism and higher macrophage inflammatory response with release of pro-inflammatory cytokines (interleukin-1 (IL-1), IL-6 and tumour necrosis factor-a). Hypothyroidism may cause symptoms such as fatigue, myalgia and arthralgia that may also occur in RA. One study, of 52 prevalent RA patients, reported a correlation between hypothyroidism and higher disease activity. Another study, based on 439 prevalent RA patients from a Danish registry and based on 28-joint Disease Activity Score-C reactive protein (DAS28-CRP) scores reported, somewhat contradictory, no significant difference in RA disease activity at diagnosis but a reduced chance of response to anti-rheumatic drugs at 4 months from treatment initiation. These findings call for a more detailed assessment of how AITD impacts the presentation and evolution of RA disease activity, as measured by different types of metrics, and also of how AITD affects the observed RA treatment response.

The objectives of this study were therefore to investigate, in a study population large enough to allow for assessments of differences across subgroups of patients, whether and how concomitant AITD impacts patient-related and physician-related measures of disease activity, at the time of RA diagnosis and at 3-month and 6-month follow-up visits, and also how AITD affects the response to first-line treatment with methotrexate. In addition to overall effects, we investigated variations in RA disease presentation and treatment response across subsets as defined by RA serological status, sex and age.

PATIENTS AND METHODS
Setting and data sources
The setting and data sources used for this study have been described in detail previously. Following RA diagnosis, the majority of Swedish RA patients start methotrexate as their first disease-modifying anti-rheumatic drugs (DMARD). The dose of methotrexate is increased up to 20 mg per week. Patients are followed-up according to an early RA treatment guideline (see eText 1 in online supplementary material). In brief, we used data from the following sources: The Swedish Rheumatology Quality Register (SRQ) is a nationwide clinical register of patients with RA. It is used in clinical practice since 1996 to follow patients’ disease course longitudinally, including anti-rheumatic treatments, health-related variables and the physicians and patients’ assessment of disease activity. The current coverage is close to 90% of all new-onset RA. To be registered as ‘early RA’ in the SRQ, the patient must fulfill the American College of Rheumatology classification criteria21 with a RA symptom duration less than 12 months. The Swedish prescribed drug register (PDR) started in 2005 and includes information on all dispensations of prescribed drugs in Sweden. The Swedish cancer register started in 1958 and includes all incident diagnoses of cancer and is mandatory for all clinicians.

Swedish residents are assigned a personal identification number, unique for each individual, which enables linkage of individual-level data across nationwide registers, and the current study is based on a linkage between the registers described above. The Stockholm Regional Ethics Committee approved this study (DNR 2015/1844-31/2).

Study population
We identified all patients included as early RA in the SRQ between January 1, 2006 and December 31, 2016 (n=13 187). The current analyses are based on those 9 004 patients (6 072 women and 2 932 men; mean±SD age, 65.8±15.0 years) who started methotrexate monotherapy at diagnosis and who had disease activity measures registered both at start and at follow-up visits to allow for response analyses, see table 1 and online supplementary figure 1. The occurrence of AITD among excluded patients did not differ substantially from those included.

Occurrence of AITD
The vast majority of patients treated with thyroxine substitution have an underlying AITD, once non-autoimmune causes for treatment are excluded. We therefore defined AITD as filling a prescription of thyroid hormone substitution therapy, identified through linkage to the PDR 2005 through 2016. Patients with a prescription of iodine-containing drugs (interferon-alpha, lithium and amiodarone) or a previous thyroid cancer, based on linkage to the PDR and the Swedish Cancer Register were excluded (see eText 2 for the ATC and ICD codes used and online supplement tary figure 1). Prevalent AITD was defined as a thyroxine prescription in the PDR already before the diagnosis of RA.

RA disease activity and treatment response
We used DAS28-erythrocyte sedimentation rate (ESR) to define RA disease activity and the change in RA disease activity between visits, ΔDAS28-ESR, at the 3-month or 6-month visit after treatment start (±1–2 months). If the patient had several visits during the specified time period, we used the visit closest to 3 and 6 months from the time of diagnosis, respectively.

Response states were defined as non, moderate and good responder based on the EULAR DAS28-ESR response criteria. In addition, a patient was defined as non-responder if switching from methotrexate to another DMARD at or before the follow-up visit, irrespective of EULAR response status. Below, DAS28-ESR will be referred to as DAS28.

In addition to the patient global Visual Analogue Scale (VAS) (below referred to as ‘patient global’), we used the

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Table 1  Baseline characteristics of 9004 RA patients identified in the Swedish Rheumatology Quality Register (SRQ), 2006–2016

| Characteristics | Overall (n=9004) | AITD+† (n=1003) | AITD–† (n=8001) |
|-----------------|-----------------|-----------------|-----------------|
| Sex             |                 |                 |                 |
| Women           | 6072 (67.4)     | 886 (88.3)      | 5186 (64.8)     |
| Men             | 2932 (32.6)     | 117 (11.7)      | 2815 (35.2)     |
| Age at inclusion in SRQ/index date‡ | 65.8 (15.0) | 68.3 (14.1) | 65.5 (15.1) |
| RA diagnosis§   |                 |                 |                 |
| Seropositive RA | 6088 (67.6)     | 694 (69.2)      | 5394 (67.4)     |
| Seronegative RA | 2687 (29.8)     | 272 (27.1)      | 2415 (30.2)     |
| Unspecified RA  | 229 (2.5)       | 37 (3.7)        | 192 (2.4)       |
| Duration of symptoms (months) | 5.5 (3.3) | 5.5 (3.3) | 5.5 (3.3) |
| Year of inclusion in SRQ | | | |
| 2006            | 690 (7.7)       | 68 (6.8)        | 622 (7.8)       |
| 2007            | 699 (7.8)       | 65 (6.5)        | 634 (7.9)       |
| 2008            | 747 (8.3)       | 81 (8.1)        | 666 (8.3)       |
| 2009            | 914 (10.2)      | 89 (8.9)        | 825 (10.3)      |
| 2010            | 812 (9.0)       | 94 (9.4)        | 718 (9.0)       |
| 2011            | 835 (9.3)       | 94 (9.4)        | 741 (9.3)       |
| 2012            | 891 (9.9)       | 113 (11.3)      | 778 (9.7)       |
| 2013            | 872 (9.7)       | 102 (10.2)      | 770 (9.6)       |
| 2014            | 834 (9.3)       | 95 (9.5)        | 739 (9.2)       |
| 2015            | 846 (9.4)       | 92 (9.2)        | 754 (9.4)       |
| 2016            | 864 (9.6)       | 110 (11.0)      | 754 (9.4)       |

*Values are the number (%).
†First thyroxine prescription before RA diagnosis. Non-autoimmune case for thyroxine prescription not excluded.
‡Mean (± SD years).
§According to the ICD 10 registered, assessed at the time of inclusion in the SRQ.
AITD, autoimmune thyroid disease; RA, rheumatoid arthritis.

and the change (delta) of the parameter between the RA diagnosis and the 3-month and 6-month follow-up visits, respectively, using linear regression, with models adjusted for age and sex, as well as additionally adjusted for the baseline value of the parameter in question.

Third, we examined the association between AITD and response to methotrexate after 3 and 6 months from treatment initiation by comparing the proportions of EULAR DAS28 good responders versus moderate or non-responders, using logistic regression adjusted for age and sex. In additional models, we also adjusted for HAQ, use of oral steroids and smoking.

All analyses were performed by using SAS version 9.4 (SAS Institute).

Because of missing values (approximately 20%, see eText 3 in online supplementary material) on the DAS28 variables, we performed two separate analyses, one for all patients with a 3-month and/or 6-month visit (n=6025 and n=4996) and one for the patients with complete information on DAS28 variables at the same time points (n=3831 and n=4100; online supplementary figure 1). The proportions of patients receiving methotrexate or prednisolone at start and 3/6 months and response status were similar for the patients with versus without complete information on DAS28. The characteristics of patients with complete information on DAS28 are shown in Table 2. We further imputed response status for those patients who had missing information on EULAR DAS28 response by multiple imputations (see eText 3 in online supplementary material). We similarly imputed data on HAQ and smoking.

### RESULTS

Among the 9 004 RA patients who were included in the study, the prevalence of AITD was 11% (n=1 003) (Table 1). As expected, the proportion of women was higher in patients with AITD compared with those without (88% vs 65%), while the mean±SD age did not differ substantially between the groups (68±14 vs 65±15 years).

AITD and its association with disease activity at RA diagnosis and at 3/6 months

At RA diagnosis, the patient-reported disease activity measures (patient global, HAQ and pain) were significantly higher among RA patients with AITD compared with those without: patient global 57 vs 52, mean difference +3.6, HAQ 1.2 vs 1.0, mean difference +0.08, pain 58 vs 53, mean difference +3.8. The DAS28 levels were clinically and statistically similar in patients with versus without AITD (5.2 vs 5.1, mean difference +0.1), see Table 3. Among the individual DAS28 components, ESR, swollen joint count and tender joint count were not statistically higher in patients with versus without AITD, Table 3. At 3 and 6 months, there were only small numerical and no statistical differences in all of the above measures between patients with versus without AITD (Table 3 and online appendix Table I).
AITD and change in RA disease activity between baseline and 3/6 months

Comparing baseline and 3 months, patients with (vs without) AITD had a more pronounced decrease in patients global (−28 vs −24), whereas the decrease in pain, HAQ and other DAS28 components was similar (table 4). The change in DAS28 components is displayed in figure 1. Comparing baseline and 6 months, there were only small numerical differences, for all parameters under study (table 4). When adjusting also for the baseline value of the parameter under study, the difference in delta patients global for those with versus without AITD disappeared, but for all other parameters, the pattern of small differences remained (online appendix table II).

In analyses stratified by age at RA diagnosis, the ten or so percent of all patients who were below 45 years of age displayed a somewhat different pattern, with AITD linked to a slightly lower disease activity at baseline, though none of these differences reaches statistical significance (online appendix tables III and IV).

| Table 3 | DAS28 parameters at baseline and at 3-month follow-up visit for RA patients in the Swedish Rheumatology Quality Register (SRQ), 2006–2016 |
|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|
| **Patients with complete information at 3-month follow-up visit (n=4 831)** | **Patients with complete information at 6-month follow-up visit (n=4 010)** |
| **Baseline** | **3-Month follow-up** | **Baseline** | **6-Month follow-up** |
| Methotrexate | 4 831 (100) | 4 497 (93) | 4 010 (100) | 3 579 (89) |
| Prednisolone | 3 144 (65) | 2 984 (62) | 2 604 (65) | 2 311 (58) |
| **Response status†** |  |  |  |  |
| Non-responders | 1 382 (29) | 1 576 (39) |  |  |
| Moderate responders | 1 284 (27) | 776 (19) |  |  |
| Good responders | 2 165 (45) | 1 658 (41) |  |  |

*Values are the number (%).
†Response status according to EULAR response criteria. If change of DMARD at follow-up visit=non-responder.

RA, rheumatoid arthritis.

For each of the seven variables named in the first column and for each time point, the estimate (β) was provided by a linear regression model for which the variable in the first column was the dependent variable, AITD the independent variable, and age and sex used as adjustment. The estimate β gives the mean difference (given the linear model) between the two types of patients, a positive value meaning that the AITD+ patients have on average a higher value than the AITD− patients.

AITD, autoimmune thyroid disease; DAS28, 28-joint Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; RA, rheumatoid arthritis; SJC, swollen joint count; TJC, tender joint count; VAS, Visual Analogue Scale.
Among 7,442 RA patients starting MTX, 6,025 had a 3-month follow-up visit and 4,996 had a 6-month visit (see online supplementary figure 1). Disease activity measures were registered or imputed (registered for 4,831 and imputed for 1,194 patients) at both diagnosis (treatment initiation) and the 3-month follow-up visit. Overall, we observed no difference in the proportion of patients with concurrent AITD among the non/
1.10 (table 5). At 6 months, there was a significant but not in older patients, OR, 0.92; 95% CI, 0.77 to lower chance of good response among younger 

Table 5  Association between autoimmune thyroid disease and response to methotrexate at 3-month follow-up visit among 
6025 RA -patients (3 395 non/moderate responders, 2 630 good responders) in the Swedish Rheumatology Quality Register 
(SRQ), imputed dataset

| AITD in non/moderate responders (n)* (cases) | AITD in good responders (n)* (controls) | OR (95% CI)† | OR (95% CI)‡ |
|------------------------------------------------|----------------------------------------|--------------|--------------|
| Overall 376 (11) | 286 (11) | 0.95 (0.80–1.13) | 0.93 (0.78–1.10) |
| Sex
| Women 336 (14) | 248 (15) | 0.93 (0.78–1.12) | 0.90 (0.75–1.08) |
| Men 40 (4) | 38 (4) | 1.05 (0.66–1.69) | 1.03 (0.64–1.66) |
| Age group
| <45 years 30 (9) | 17 (6) | 1.44 (0.76–2.76) | 1.43 (0.74–2.75) |
| ≥45 years 346 (11) | 269 (11) | 0.92 (0.77–1.10) | 0.89 (0.75–1.07) |
| Serostatus
| RF and/or ACPA positive 265 (11) | 192 (11) | 0.99 (0.81–1.22) | 0.95 (0.78–1.17) |
| RF and ACPA negative 97 (10) | 81 (10) | 0.86 (0.62–1.20) | 0.85 (0.60–1.18) |
| Serostatus unspecified 14 (20) | 13 (16) | 1.19 (0.50–2.84) | 1.49 (0.59–3.72) |

According to EULAR response criteria including imputed values on response status. Values are the numbers (%).
†Adjusted for age and sex.
‡Adjusted for age, sex, cortisone, HAQ, smoking. Multiple imputations=50.
AITD, autoimmune thyroid disease; HAQ, Health Assessment Questionnaire Disability Index; RA, rheumatoid arthritis.

DISCUSSION

Our results from this large study on the impact of AITD on RA disease presentation and response, indicate that AITD affects disease presentation at RA diagnosis, primarily through patient-reported but not objective measures. Taking this difference into account, AITD did not seem to affect the chance of receiving a good treatment response. These findings underscore the need for a systematic evaluation of not only composite measures such as DAS28 levels but also of its individual components and additional parameters. In contrast to this overall pattern, we noted a somewhat different pattern of disease activity and a stronger negative effect on treatment response, in patients with AITD and below 45 years of age. These latter results extend previous findings of a stronger link between AITD and RA among younger patients (the OR for hypothyroidism in RA patients, 18–44 years of age: 2.12, OR among 45–69 years: 1.42, and OR 70+ years: 1.37).9

In light of the age and sex distributions in our study population, the prevalence of AITD of approximately 11% is in line with previous results.6 13 26

One prior study, with a different design, has addressed the question whether thyroid dysfunction relates to disease activity in RA.17 However, this was a cross-sectional study in established RA using levels of thyroid-stimulating hormone (TSH >4.2 µIU/mL) as the exposure, which was present in 38% of the 52 prevalent RA patients. They found higher disease activity parameters (DAS28 and ESR) in patients with elevated TSH.18

Our findings partly corroborate those of Emamifar et al, of 439 RA patients with established RA, who compared disease activity (DAS28-CRP) in RA patients with and without hypothyroidism at treatment initiation. The individual DAS28 components were not evaluated. Treatment response measured as delta DAS28-CRP and DAS28-CRP at 4 months was significantly lower among RA-patients with thyroid disorders.18 We extend these findings by demonstrating that they are mainly explained by higher patient-related disease activity parameters at baseline. Differences compared with our study include the study design (patients were not defined as early RA, the treatment was not restricted to methotrexate, thyroid dysfunction was based on hospital records) and the statistical approach.

Several susceptibility genes involved in the pathogenesis of both AITD and RA have been identified, including PTPN22 (protein tyrosine phosphatase non-receptor type 22), CTLA4 (cytotoxic T-lymphocyte-associated leucocyte antigen) and the HLA gene
Achievement of disease control within 3–6 months after initiation of RA-treatment has been shown to correlate well with long-term outcome. Therefore, it is important to identify potential outcome predictors, and common co-morbidities in RA are important candidates, that might capture differences in underlying pathogenic mechanisms, which in turn may relate to clinical disease activity. AITD is of special interest there, since the symptoms of undertreated AITD may overlap with RA symptoms. Based on our results, concomitant AITD only has marginal impact on disease activity and response overall, but RA patients with AITD do have somewhat higher patient reported outcome measures at diagnosis, supporting that measures that may reflect both conditions in a way (patient’s global health, pain and function) can be higher in this subgroup, thereby AITD does have an influence on the phenotypic presentation of RA. In turn, this impacts the treatment response criteria used in clinical practice. The interpretation of treatment response should be seen in this light. Thus, when treating and evaluating early RA patients, those 10% with AITD in particular, it is of importance to pay attention to not only to overall disease activity and response measures such as DAS28 but to unpack its components.

Author affiliations
1Division of Clinical Epidemiology Unit, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden
2Karolinska Hospital, Stockholm, Sweden
3Faculty of Medicine, University of Iceland School of Health Sciences, Reykjavik, Iceland

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

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