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ORIGINAL ARTICLE

First-degree relatives of axial spondyloarthritis patients of the pre-SpA cohort would consider using medication in a preventive setting

Janneke J. de Winter[1] · Henriëtte M. de Jong[1] · Pythia T. Nieuwkerk[2] · Irene E. van der Horst-Bruinsma[3] · Dominique L. Baeten[1] · Marleen G. van de Sande[1]

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Abstract

To study the willingness of first-degree relatives of axial spondyloarthritis (axSpA) patients to use preventive medication. First-degree relatives of HLA-B27-positive axSpA patients (pre-SpA cohort) ($n = 106$) completed a survey including scenarios varying in disease risk, side effects, and treatment effect of hypothetical preventive medication and questions about their perceived risk of developing SpA and assessment of the severity of SpA. The willingness to use preventive medication was 63.2–91.5% (with 30–70% SpA risk, respectively) and declined to 27.4–51.9% respectively, when side effects might occur. On a visual analogue scale (VAS) 0–100 mm (totally disagree-totally agree) (median;range), participants were not occupied by the thought of developing SpA (23;13–39), did not assume that they will eventually develop SpA (22;14–35), and consider SpA a severe disease (66;52–78). The willingness to use preventive medication was negatively influenced by their own risk assessment of developing SpA (OR = 1.17, $p = .001$) and was not primarily influenced by costs and route of administration. First-degree relatives of axSpA patients with a clearly increased disease risk (70%) would largely consider using preventive medication. Their willingness roughly halved by the possible occurrence of side effects. Participants' perceived risk to develop SpA and their assessment of the severity of SpA negatively influenced the willingness to use preventive medication.

Keywords Axial spondyloarthritis · Preventive medication · Primary prevention

Introduction

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease affecting the spine, peripheral joints, and extra-articular sites. Early treatment of axSpA is important, since a delayed start of treatment is linked to worse clinical outcome [1, 2].

In rheumatoid arthritis (RA), improving outcome was gained by early and aggressive treatment, which is nowadays standard of care [3]. Moreover, attempts have been made [4] and trials are ongoing initiating treatment in the pre-clinical phase before the onset of clinical manifestations [5, 6] aimed at preventing RA. In RA it has been shown that high-risk individuals would consider using medication in a preventive setting [7]. In axSpA, little is known about the possibilities, effects, and desirability of early treatment, merely because of the difficult diagnostic process and lack of a reliable biomarker [8]. One of the risk factors to develop axSpA is having a positive family history for SpA, with a risk of 8% [9].

Initiatives as the pre-SpA cohort [10], a prospective cohort of healthy first degree relatives of axSpA patients, and the SPACE (SPondyloArthritis Caught Early) cohort [11] might enable in a very early phase to identify, treat and thereby possibly even prevent axSpA. Therefore, also in axSpA, preventive treatment is an imaginable scenario.

Janneke J. de Winter and Henriëtte M. de Jong contributed equally to this work.

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✉ Marleen G. van de Sande
m.g.vandesande@amc.uva.nl

[1] Amsterdam UMC, Department of Clinical Immunology and Rheumatology, Amsterdam Rheumatology & Immunology Center (ARC), Academic Medical Center/University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, Netherlands

[2] Amsterdam UMC, Department of Medical Psychology, University of Amsterdam, Meibergdreef 9, Amsterdam, Netherlands

[3] Amsterdam UMC, Department of Rheumatology, Amsterdam Rheumatology & Immunology Center (ARC), Vrije Universiteit Amsterdam, De Boelelaan, 1117 Amsterdam, Netherlands

To our knowledge, the willingness of first-degree relatives of axSpA patients to start preventive therapy has never been explored. If we know whether and under what circumstances at-risk individuals are willing to start preventive therapy, development of preventive treatment strategies could be targeted to that purpose.

The aim of this study was to investigate the willingness of individuals at increased risk of developing axSpA to initiate preventive treatment and evaluate which factors influence this decision.

Materials and methods

Study population

For this study, all participants from the pre-spondyloarthritis (Pre-SpA) cohort, known to have an increased risk to develop SpA, were approached regardless of their time of follow-up. This cohort has been described in detail previously [10]. In short, pre-SpA is an ongoing, prospective, multicenter inception cohort of healthy, first-degree relatives of HLA-B27-positive axSpA patients between 18 and 40 years of age. All were (1) not diagnosed as having SpA at the time of the baseline visit and (2) not treated for back pain by a physician. All participants gave their written informed consent and the ethics board of the Academic Medical Center Amsterdam approved the study protocol (Nl41248.018.12).

Survey

Participants completed a paper survey designed to assess their willingness to use treatment to prevent or delay the onset of SpA (Supplement 1). The survey comprised six scenarios. In each scenario, we changed one variable: (1) the likelihood of developing SpA varying from 30 to 70%; (2) the effectiveness of treatment; either complete prevention or 10 year delay of onset of SpA; (3) potential side effects, varying from none to mild to potential infections. For each scenario, the participant could answer to what degree he or she wants to (hypothetically) initiate preventive treatment on a 5-point Likert scale (from "no" to "yes"). We also included a question to investigate the most important factor for participants to decline using preventive treatment (partly multiple choice, partly open). Furthermore, participants scored their perception of the severity of SpA, their own risk to develop SpA, and whether they are preoccupied with the thought of developing SpA on a visual analogue scale (VAS) from 0 (totally disagree)-100(totally agree). We conducted think-aloud interviews with SpA patients, healthy volunteers with a wide variety of age and educational level, and medical doctors and nurses to verify realistic and clear scenarios and questions.

Statistical analyses

Baseline data are presented as numbers (%) (categorical data) or the mean/median (SD/IQR/range) (continuous data) as appropriate. The data on treatment preference are shown as percentages and analyzed using the McNemar's test, enabling to compare two scenarios as paired data. To prepare the data for that analysis, the "preference for treatment" outcome variable was dichotomized. A preference for treatment (the answers "Yes" and "I probably would") was assigned a score of 1, and a neutral preference ("I don't know) or preference for non-treatment ("I would probably not" and "no") was assigned a score of 0.

To test for possible interactions of willingness to use preventive medication with age, gender, HLA-B27 status, and the presence of back pain throughout the different scenarios, we used a generalized estimating equations (GEE) model with a logit link, binomial distribution, and an exchangeable correlation. GEE enables analysis of repeatedly assessed preference scenarios. It corrects for the fact that patients' answers to each subsequent scenario are related to their answers in previous scenarios. Outcome measures of the GEE were odds ratios and 95% confidence intervals. We calculated whether age, gender, HLA-B27 status, or the presence of back pain was significant predictors for (non)treatment preference.

We tested the correlation of disease perception (the own risk assessment of developing SpA) with the willingness to start using preventive medication in a linear regression model.

We performed all analyses in SPSS version 24.0.

Results

Study population and response

The study population has been described in detail earlier [10]. Of all 130 pre-SpA participants, 106 completed the survey (response rate 81.5%). Baseline characteristics are shown in Table 1. There were no missing values. Baseline characteristics between responders and non-responders did not differ (data not shown).

Evaluating participants' believes and perceptions of SpA (VAS 0–100, where 0 is defined as totally disagree and 100 as totally agree) showed that they were not occupied by the thought of developing SpA (median 23, range 13–39), did not assume that they will eventually develop SpA (median 22, range 14–35), and consider SpA as a severe disease (median 66, range 52–78).

The willingness to use preventive medication

The percentage of participants willing to use preventive medication with 100% effectiveness causing no side effects varied between 63.2% (with 30% SpA risk) and 91.5% (with 70% SpA risk) ($p < .0001$, Fig. 1).

Table 1 Baseline characteristics of participants

	Participants ($n = 106$)
Age, mean (SD)	28.7 (5.6)
Gender male, *n* (%)	47 (44)
Back pain, *n* (%)	58 (55)
HLA-B27 positive, *n* (%)	55 (52)
Current smoker, *n* (%)	24 (22.6)
Current NSAIDs use, *n* (%)	6 (5.7)
Current biologicals use, *n* (%)	1 (0.9)
Current other medication, *n* (%)	31 (29.2)
Strenuous physical exercise (work or sport related), *n* (%)	57 (53.8)
BASDAI, median (IQR)	1.0 (0.5–2.0)
CRP, median (IQR)	1.3 (0.7–2.7)
ESR, median (IQR)	5 (2–9)
Enthesitis, *n* (%)	4 (4)
Arthritis, *n* (%)	4 (4)
Dactylitis, *n* (%)	0
Psoriasis, *n* (%)	3 (3)
Inflammatory bowel disease, *n* (%)	1 (1)
Uveitis, *n* (%)	2 (2)
Reactive arthritis, *n* (%)	0

HLA-B27 human leukocyte antigen B27, *BASDAI*, Bath Ankylosing Spondylitis Disease Activity Index, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *IQR* interquartile range

The willingness of participants to use preventive medication decreased with the possible occurrence of side effects. The willingness decreased from 63.2 to 27.4% (in case of the possible occurrence of mild side effects) and to 32.1% (in case of the possible occurrence of infections) (with 30% SpA risk, both $p < .001$, Fig. 2). The willingness decreased from 91.5 to 51.9% with 70% SpA risk if infections would possibly occur ($p < .0001$, Fig. 3). When medication would cause a delay in SpA onset of 10 years (with 70% SpA risk), the percentage willing to use preventive medication decreased from 91.5 to 67.9% ($p < .0001$, Fig. 3).

The willingness to use preventive medication was inversely associated with the participants' presumption of the risk to develop SpA themselves (OR = 1.17, $p = .001$). The GEE model showed no correlation between choice for preventive medication and age (OR 1.0, $p = .96$), HLA-B27 positivity (OR 1.45, $p = .69$), or the presence of back pain (OR 1.17, $p = .58$).

The willingness to use preventive medication was primarily influenced by the certainty of the risk to develop SpA (34.0%), followed by the risk of side effects (32.1%), and the effectiveness of the medication (25.5%). Medication costs (0.9%) and the route of administration (0%) had no influence.

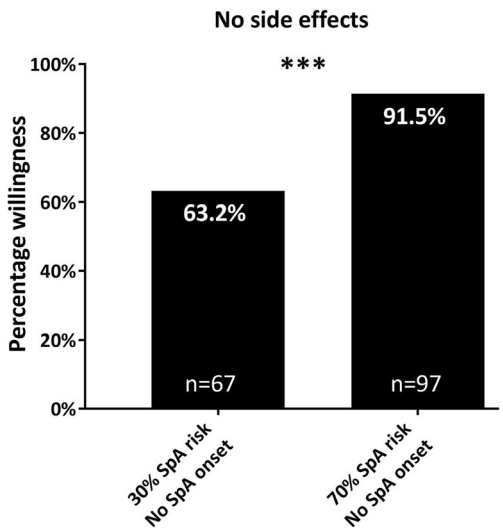

Fig. 1 Percentage of participants willing to use preventive medication without side effects ***$p < 0.0001$. The percentage of first-degree relatives of axSpA patients that is willing to use preventive medication without any side effects and with 30 or 70% risk of ever developing SpA. axSpA, axial spondyloarthritis; SpA, spondyloarthritis

Discussion

The results of our study suggest that (1) 67% of individuals at increased risk to develop SpA is willing to use preventive medication when the hypothetical risk to develop SpA is 30%, increasing to 97% when this risk is 70%, if the medication would not cause any side effects. (2) Potential side effects lower the willingness to use preventive medication to 27% and 52% with 30% and 70% disease risk, respectively. And (3) the

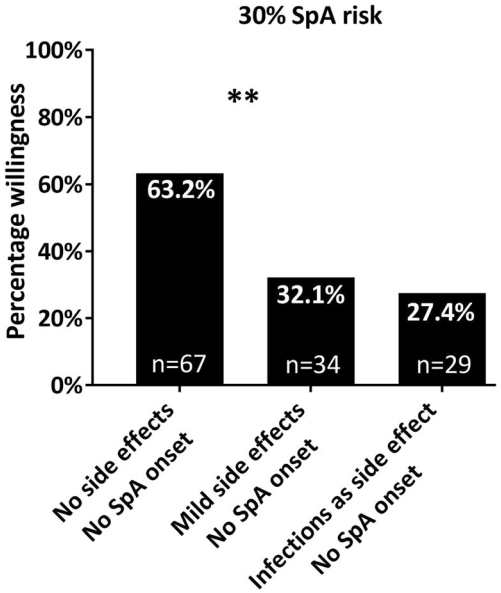

Fig. 2 Percentage of participants willing to use preventive medication with 30% risk of developing SpA **$p < 0.001$. The percentage of first-degree relatives of axSpA patients that is willing to use preventive medication with a 30% risk of ever developing SpA and with either none, mild side effects or infections as a side effects, all with a 100% effectiveness of the medication. axSpA, axial spondyloarthritis; SpA, spondyloarthritis

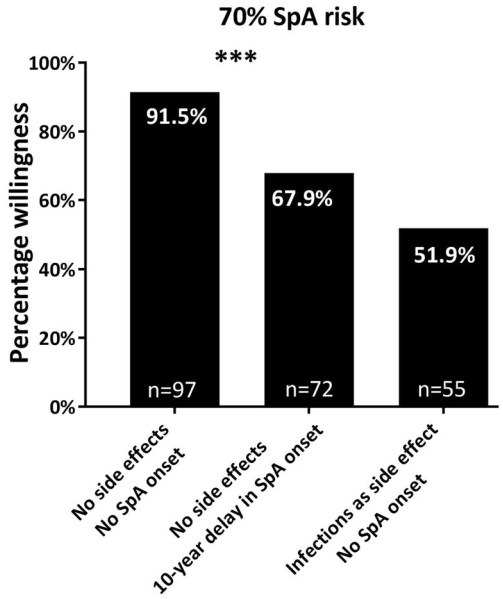

Fig. 3 Percentage of participants willing to use preventive medication with 70% risk of developing SpA***$p < 0.0001$. The percentage of first-degree relatives of axSpA patients that is willing to use preventive medication with a 70% risk of ever developing SpA and with either no side effects and no onset of SpA, no side effects and a 10-year delay of SpA onset, or infections as a side effect and no SpA onset. axSpA, axial spondyloarthritis; SpA, spondyloarthritis

willingness to use preventive medication is influenced by the participants' own perception of the severity of the disease and the disease risk, regardless of the given hypothetical risk.

In a previous study in RA using a comparable study population, approximately one third of the participants chose to take preventive medication if the risk of developing RA was 20–40%, with a varying risk of side effects [7]. This is concordant with the findings of our study that approximately 30% of participants is willing to use medication with a 30% risk of developing SpA and the possibility of side effects.

Studies to investigate the willingness of individuals to use medication in a preventive setting have been performed in other diseases than axSpA. Port et al. investigated the willingness of women eligible to use tamoxifen for breast cancer prophylaxis, and showed that the vast majority declined because of side effects [12]. Another study performed in Denmark investigated whether individuals would use preventive treatment for cardiovascular disease; in this study, more than half of respondents who were initially willing to use this medication declined after hearing about side effects [13]. Interestingly, in our study, the willingness to use preventive medication also dropped by 50% when mild side effects might occur, despite the fact that these side effects would stop directly after quitting the preventive medication. Together with our study results, these results emphasize the importance of thorough education of at-risk individuals with regard to their risk profile and the preventive therapy that is offered.

Our study has several strengths. First, the Pre-SpA cohort is by our knowledge the only cohort of first-degree relatives (FDRs) of axSpA patients, representing a unique opportunity to study a population at increased risk for developing SpA. Second, the high response rate (81.5%) suggests that the subject is of relevance for participants.

Our study has also limitations. First, some of the theoretical values that were used in this study are extremes (e.g., the efficacy of medication (100%) and risk to develop SpA (70%)). However, the scope of this study is not to deduct a fixed willingness, but to conclude that there is a reasonable willingness that is fluctuating with the magnitude of the risk to develop SpA, the risk to develop side effects and the effectiveness of the medication. Previous research showed that participants may encounter difficulties in interpreting percentages and complex hypothetical scenarios [14]; therefore, we chose a limited amount of scenarios and chances. Second, FDRs of axSpA patients included in pre-SpA might be more inclined to take preventive medication than non-participating FDRs because of symptoms possibly relating to SpA. This suggestion is contradicted by the fact that the willingness to use preventive medication is not influenced by HLA-B27 status or by the presence of back pain. Moreover, data between participants and non-participants did not differ, suggesting that the data are representative for the study population. Third, despite being composed thoroughly, we might have not included all important variables in our study scenarios. For example, our study did not show a difference in willingness to use preventive medication between men and women, whilst in daily practice, women might fear to be unable to get pregnant because of certain therapies (although of note, the fear of becoming infertile can be experienced by both women and men). At some point, we had to compromise between length and clarity of the survey and completeness.

In conclusion, when the axSpA risk is clearly increased (70%) or when preventive medication has no side effects, the vast majority of first-degree relatives of axSpA patients seems willing to use preventive medication. This willingness roughly drops by 50% by the possible occurrence of mild side effects.

Further research will have to focus on highly effective medication with an acceptable safety profile and on selecting individuals at clearly increased risk to develop SpA.

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Compliance with ethical standards

All participants gave their written informed consent and the ethics board of the Academic Medical Center Amsterdam approved the study protocol (Nl41248.018.12).

Conflict of interest DB is an employee of UCB pharma. The other authors declare that they have no competing interests.

Abbreviations Pre-SpA, pre-spondyloarthritis; axSpA, axial spondyloarthritis; VAS, visual analogue scale; SpA, spondyloarthritis; RA, rheumatoid arthritis; HLA, human leukocyte antigen; GEE, generalized estimating equations; FDR, first-degree relative

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