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Drug consumption in the first years of rheumatoid arthritis in France, the Netherlands, and Norway

A longitudinal study in the early nineties

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Objective: To analyse drug consumption in the first years of rheumatoid arthritis (RA) in France, the Netherlands, and Norway, in a longitudinal study between 1991 and 1993.

Patients and Methods: The EURIDISS cohort followed up over three years included 695 RA subjects with less than 5 years disease duration. Clinical and biological parameters, drug consumption according to ATC classification, and use of local treatment were recorded.

Results: In the Netherlands consumption of second-line treatment occurred early on, and remained constant over time. In France, it was consumed by half of the subjects and decreased during follow-up (p<0.001). In Norway, 50% of the subjects were on second-line treatment at the outset. NSAIDs rather than corticoids were the most widely consumed. Patients underwent frequently local treatments with decrease frequency of infiltrations over time (p<0.001).

Conclusion: Second-line treatments were used in the first years of disease development, following varying sequences in the different countries.

Key words: rheumatoid arthritis, treatment, consumption, drugs

Rheumatoid arthritis (RA) can cause severe functional disability in the long term despite a large range of therapeutic strategies (1–3). One could wonder how far drug consumption may vary across country or practice settings.

Until the 80s, therapeutic strategy in the first years of RA was frequently cautious and generally followed the “therapeutic pyramid”. Thus, at the outset, only NSAIDs were prescribed, followed two or three years later by second-line treatment which were only partially effective, and aggressive treatments combined with corticoids were only introduced at a later stage (4, 5). At the beginning of the nineties, immuno-modulators which included methotrexate were introduced and the treatment of early RA was reviewed in the light of this development (6). There are few studies on routine therapeutic practice and at the start of the 90s there had been no comparisons in treatment strategies among European countries (7). The doctor’s prescription does not reflect actual treatment. None have reported on patient consumption in this period.

The objective of this study is to describe the consumption of second line treatment, anti-inflammatory drugs, local interventions, and surgery in the first years of RA and over 3 years of disease follow up from 1991 to 1993 in France, the Netherlands, and Norway, on the basis of the EURIDISS cohort (8).

Materials and methods

The EURIDISS longitudinal study is a population based cohort including patients recruited from a defined geographical area, via press campaign, hospital files, and ambulatory care settings, at all levels of the care system (9). The inclusion criteria were:

- patients of either sex between the ages of 20 and 70 at study outset
- patients from the following areas: Lorraine and Champagne district in France, Groningen district in the Netherlands, Oslo and Akerhus county in Norway
- patients with RA diagnosis in accordance with ARA 87 criteria (10, 11)
- disease duration under 5 years at the time of inclusion
- informed consent

Exclusion criteria were:

- presence of other severe chronic disabling diseases
- association of RA with vasculitis at the time of inclusion
– stage IV in the Steinbrocker classification
– high risk of patient being lost to follow-up (e.g. foreseeing moving).

Among RA cases identified in each area, the non-response rate at entry varied: 12% in the Netherlands, 17.9% in Norway, and 30% in France. The age difference between responders and non-responders was greatest in the Netherlands, where non-responders were older by 8 years on average. The largest sex differences were found between the Norwegian responders and non-responders: of the former group 74% were female versus 83% of the latter. But overall, the distribution for gender and age was very similar for the two groups (9).

Data were collected in the course of two interviews within a period of two weeks, in the respondent’s home or in hospital, conducted by trained interviewers. Datasets were thus obtained by repeating this procedure once a year for three consecutive years: 1991, 1992, 1993.

The clinical data recorded included age, gender, presence of rheumatoid nodules, presence of extra-articular damage, Steinbrocker classification, sedimentation rate, and functional disability using the Health Assessment Questionnaire (HAQ) (12). Treatment received in the course of the preceding year was the medication taken and its nature as reported by the patient (second-line treatment, NSAIDs, corticoid drugs, pain killers), the number of intra-articular infiltrations whatever the location or the substance used (radionucleotides, corticoids, osmic acid), and the number of surgical acts in connection with RA whatever their nature or location. Drugs were recorded by trade names. In each country, each drug was given its chemical name (13), and a code according the Anatomical Therapeutic Chemical classification (ATC) (14). This classification comprises 5 levels. The first level is the anatomical group (e.g. skeletal and muscle system), the second is the therapeutic group (e.g. anti-rheumatic and anti-inflammatory molecules), the third is a therapeutic sub-group (e.g. non-steroid anti-rheumatic and anti-inflammatory molecules), the fourth gives the chemical form (e.g. oxicam), and the fifth the chemical sub-group (e.g. piroxicam) (15). For this study only the first three levels were used.

The statistical analysis describes the clinical characteristics of the cohort and the medicine consumption. The results are expressed as means with standard deviation and extreme values, or else as frequencies. A time and a country effect for drug consumption differences was tested using Cochrane-Armitage trend test. Detailed comparisons between countries and between years were performed by variance analysis for quantitative variables and by a Chi2 test for qualitative variables.

Results
Clinical description of the cohort (Table I)
Among 695 subjects included in 1991, the cohort study comprised 628 subjects follow-up of whom 131 were French, 277 Dutch, and 220 Norwegian, while 9.6% were lost to follow-up over the three years (34 French, 15 Dutch, and 18 Norwegians). These dropouts were related to deaths, moving outside the catchment area, changes in diagnosis, or refusals.

The average disease duration at entry of patients was 2.1 years.

There were several statistical significant differences from one country to another. In 1991, 13.5% of the subjects showed rheumatoid nodules. Three years later, the French and Norwegians had twice the percentage as the Dutch. Extra-articular signs were rare in the Netherlands, more frequent in the two other countries.

In France and the Netherlands the average HAQ score was near 1 at all three assessments. It was higher in Norway at 1.6 (p<0.01).

Overall medicine consumption
The overall medicine consumption was stable over the period of follow up, except for a significant decrease in France (p<0.002) (Table II).

In 1993, in France, 25.4% were only taking one drug and 38.7% had no medication.

Medical consumption (ATC classification)
The description of drug consumption is given per therapeutic group and sub-group in Table III.

Second-line treatment. There are differences in second-line medication from one country to the other (p=0.001), but no significant time effect over the follow-up.

In 1991, 58% of the French subjects were receiving second-line medication. Thereafter, this figure is halved. In the Netherlands and in Norway, the overall recourse to second-line therapy is larger for all three assessments (Netherlands: 69% in 1991 to 81% in 1993; Norway: 52% in 1991 to 44% in 1993).

In France, Hydroxychloroquine and Injectable Gold salts were the most frequently reported second line drugs in 1991 (26% for each). In 1993, methotrexate became the most widely used of all
second-line treatments. In the Netherlands, hydroxychloroquine accounted for 31% of second-line drugs used in 1991, followed by sulfasalazine and gold salts. Methotrexate represented only 3% of second-line treatments. In 1993 sulfasalazine headed the list of second-line drugs at 30%, methotrexate showed an increased share at 12%. For the Norwegian cohort, from the study outset in 1991 methotrexate was the most widespread drug in use, and accounted for 34% of second-line therapies, reaching 45% in 1993. Sulfasalazine and orally administered gold salts are the other two most commonly reported substances. Thus, each country has its particular consumption practice of second-line therapy. Apart from the instance of gold salts for 1991, there was a significant difference in consumption for the various second-line drugs (methotrexate: \( p < 0.00001 \); sulfasalazine: \( p < 0.0001 \); hydroxychloroquine: \( p < 0.0001 \)).

The way in which consumption of each drug evolved was studied over time (Table IV). Around 20% of the French, 55% of the Dutch, and 28% of the Norwegians were taking second-line drugs at the time of all three assessments (permanent consumer). Conversely, 32% of the French, 4% of the Dutch, and 12% of the Norwegian had never received any (never consumer). The remaining subjects were considered as occasional consumer.

In France, at all three assessments only 3.6% of the subjects consumed gold salts. Few subjects started second line treatment in 1992 or 1993. Where they did, the drug that was most often used was methotrexate (6% in 1992 and 3% in 1993). In the Netherlands 9.5% of the subjects were receiving gold salts at the time of all three assessments. In Norway 4.6% of the subjects were taking gold salts at all three assessments. Methotrexate was being used by 8.8% of subjects at all three assessments, and was in addition started up in 1992 for 6.3% and in 1993 for 4.6% of subjects. Apart from gold salts, the way in which the consumption of second line drugs evolved in the three countries differs (methotrexate: \( p < 0.003 \); hydroxychloroquine: \( p = 0.004 \); sulfasalazine: \( p = 0.001 \)).

**NSAIDs.** Consumption of NSAIDs therefore varied significantly from country to country (\( p < 0.0001 \)), without homogenous time effect.

In France, 66% of the subjects were using NSAIDs in 1991 (Table III). But this had fallen to 31% in 1993.

In the Netherlands, the consumption of NSAIDs was higher at 71.4% in 1991 and 75.7% in 1993.

In Norway, the consumption of NSAIDs was 45% on average in 1991, 40.8% in 1992, and 61% in 1993.

**Corticoids.** Behaviour towards corticoid therapy varied considerably from one country to another (\( p < 0.0001 \), and lightly over time (\( p < 0.05 \)).

In France the overall consumption of corticoid drugs over the three assessments varied around 20% (from 18.8% to 23%) of the patients.

Corticoids were less used in the Netherlands, around 10% (from 7.9% to 11.0%).

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**Table I. Clinical characteristics of patients at time of inclusion for each country in 1991.**

<table>
<thead>
<tr>
<th>Country</th>
<th>France</th>
<th>Netherland</th>
<th>Norway</th>
<th>Lost to follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>131</td>
<td>277</td>
<td>220</td>
<td>67</td>
</tr>
<tr>
<td>Females (%)</td>
<td>72</td>
<td>64</td>
<td>73.5</td>
<td>71.3</td>
</tr>
<tr>
<td>Age (years)</td>
<td>52.1 [11.7]</td>
<td>54.3 [11.8]</td>
<td>51.9 [13.0]</td>
<td>52.6 [13.2]</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>2.5 [1.4]</td>
<td>2.2 [1.1]</td>
<td>1.9 [1.1]</td>
<td>2.2 [1.3]</td>
</tr>
<tr>
<td>Rheumatoid nodules (%)</td>
<td>13.5</td>
<td>14.1</td>
<td>13.9</td>
<td>11.9</td>
</tr>
<tr>
<td>Extra-articular signs (%)</td>
<td>13.4</td>
<td>7.2</td>
<td>20.6</td>
<td>11.3</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>28.4 [25.3]</td>
<td>27.6 [23.3]</td>
<td>27.6 [19.7]</td>
<td>31.3 [26.2]</td>
</tr>
<tr>
<td>Steinbrocker I (%)</td>
<td>13.9</td>
<td>9.3</td>
<td>8.5</td>
<td>11.3</td>
</tr>
<tr>
<td>II</td>
<td>70.3</td>
<td>73.8</td>
<td>72.0</td>
<td>63.4</td>
</tr>
<tr>
<td>III</td>
<td>15.8</td>
<td>16.9</td>
<td>19.5</td>
<td>25.4</td>
</tr>
<tr>
<td>HAQ (0–3)</td>
<td>1.0 [0.7]</td>
<td>1.1 [0.8]</td>
<td>1.6 [0.3]</td>
<td>1.1 [0.8]</td>
</tr>
</tbody>
</table>

No significant difference between patients in the study and those lost to follow up.

[ ]: Standard deviation.

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**Table II. Overall medical consumption of subjects for each country over time.**

<table>
<thead>
<tr>
<th>Country</th>
<th>France</th>
<th>Netherland</th>
<th>Norway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug consumption* (%)</td>
<td>0</td>
<td>9.3</td>
<td>38.7</td>
</tr>
<tr>
<td>1</td>
<td>13.7</td>
<td>25.4</td>
<td>25.3</td>
</tr>
<tr>
<td>2</td>
<td>31.2</td>
<td>14.5</td>
<td>41.4</td>
</tr>
<tr>
<td>&gt;2</td>
<td>45.8</td>
<td>21.4</td>
<td>24.4</td>
</tr>
<tr>
<td>Surgery (%)</td>
<td>8.8</td>
<td>12.2</td>
<td>10.7</td>
</tr>
<tr>
<td>Infiltration (%)</td>
<td>38.2</td>
<td>24.4</td>
<td>30.2</td>
</tr>
</tbody>
</table>

*\( p < 0.05 \) between countries.
In Norway, about 29% of the subjects were on corticoids at each assessment (from 18.5% to 30.7%).

Intra-articular infiltrations and surgery (Table II)

There was a significant decrease in the percentage of subjects who received infiltrations over time in the three countries: 38% to 24% of subjects in France, 30% to 22% in the Netherlands, and 29% to 24% in Norway from 1991 to 1993 respectively (p<0.001), but no significant difference between countries. The number of infiltration and the dosage were not studied in details. They included straightforward cortisone infiltrations, or more aggressive treatments like isotopic synoviothresis.

For each year, about one subject out of ten for all three countries had undergone surgery in connection with rheumatoid arthritis in the preceding year. The detailed nature of interventions was not recorded. There was no significant difference over time nor among the three countries.

Discussion

This study sets out to analyse the consumption of medical treatment in Europe in the early nineties. There is no agreement in practice among the countries studied, but from the outset of this study, consumption of second-line treatment is observed. The sequence of therapies used differs from one country to another and over time in this cohort study.

Few studies have been carried out on the consumption of medication among subjects who have had RA for less than 5 years, a period for early treatment initiation. At the end of the eighties, both the idea of hard-strike treatment at the outset, and numerous publications advocating methotrexate, contributed to changes in the way medical care was envisaged (6,16,17). In a previous analysis using the EURIDISS database, it was noted that the evolution of functional disability was not linear over the first five years of RA (3). Thus, the early years of RA are the “ideal” period for starting aggressive, i.e. second-line treatment. In the course of the eighties and early nineties, methotrexate was the subject of numerous studies and was authorised for sale and use in RA (17, 18).

In order to enable comparison between countries, recruitment was carried out in a defined geographical area using identical recruitment criteria in the three countries, all levels of care provision and medical care professionals, so as to avoid a selection bias (8). The response rate was acceptable compared to cases identified in each area from incidence study in France (19), county register in Norway (20), and

| Table III. Medical consumption of subjects for each country and each year. |
|-----------------|----------------|-----------------|-----------------|----------------|
|                 | France         | Netherland      | Norway          |
| Second-line treatment (%)* | 58.0 | 33.9 | 27.3 | 69.3 | 83.0 | 81.4 | 52.0 | 53.0 | 44.0 |
| NSAIDs (%)*   | 66.0 | 36.0 | 31.5 | 71.4 | 76.8 | 75.7 | 45.8 | 40.8 | 61.0 |
| Corticoids (%)* | 23.0 | 18.8 | 20.6 | 7.9  | 9.9  | 11.0 | 28.2 | 18.5 | 30.7 |
| Mean dose (mg) in prednisone – equivalent | 8.0  | 8.1  | 6.6  | 3.3  | 7.5  | 6.6  | 8.2  | 8.9  | – |

*p<0.001 between countries.

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| Table IV. Characteristics of patient consumption of second line treatment obtained from longitudinal follow-up over 3 years (percentage of subjects involved). |
|-----------------|----------------|-----------------|-----------------|----------------|
|                 | France         | Netherland      | Norway          |
|                 | Permanent consumer | Occasional consumer | Never consumer | Permanent consumer | Occasional consumer | Never consumer | Permanent consumer | Occasional consumer | Never consumer |
| Second-line treatment (%) | 20.0 | 48.0 | 32.0 | 55.0 | 41.0 | 4.0 | 28.0 | 60.0 | 12 |
| Gold salts (%) | 3.6  | 16.3 | 80.1 | 9.5  | 15.9 | 74.6 | 4.6  | 17.7 | 77.7 |
| Hydroxychloroquine (%)* | 4.2  | 14.6 | 81.2 | 11.9 | 15.5 | 72.6 | 0.4  | 8.5  | 91.1 |
| Methotrexate (%)* | 3.6  | 16.4 | 80.0 | 2.3  | 9.3  | 90.4 | 8.8  | 20.7 | 70.5 |
| Sulfasalazine (%)* | –    | –    | –    | 9.5  | 20.3 | 70.2 | 4.2  | 10.1 | 85.7 |

*p<0.05 between countries.

Permanent consumer: taking second-line drugs at the time of all three assessments.
Occasional consumer: taking second-line drugs at one or two times of the three assessments.
Never consumer: never taking second-line drug.
hospital files in the Netherlands. No differences could be evidenced between responders and non responders among identified patients in each country. Since clinical practice may also vary considerably within the same country, we cannot conclude that our results are totally representative of each country.

All classes of drugs were studied, without restriction to second-line drugs alone. The ATC classification made it possible to make comparisons at a European level. Consumption was studied on the basis of patient reporting, by recording the medical consumption per year in each patient. This enabled estimates to be as close as possible to actual consumption, but is not fully representative of prescribing practice on the part of rheumatologists. Indeed, actual consumption is not always in line with the prescription initially made. Compliance with prescription has already been studied in the same EURIDISS cohort over the same period (21). Prescriptions were complied with in 36% of cases over the three study years. Factors for good compliance were old age, female sex, considerable damage by the disease, satisfactory relationships with the medical staff, and being well-informed about the disease.

The consumption differs between countries. In the Netherlands, the second-line drug was used early in the disease and maintained subsequently. In France, the second-line treatment was frequently used at the beginning of the disease and decreased later. In Norway, around 50% of the subjects used a second-line treatment, with a high rate of methotrexate. It can be noted that combinations of second-line drugs were rarely recorded in our study despite increasing interest and rationale for such approach (22). The heterogeneity of drug consumption frequency over time was significant after adjustment over country differences. This pertained mainly to symptom treatment by NSAIDS, corticoids, or local treatment like joint infiltration. We could not delineate whether such variation of drug consumption was related to variations in disease progression, in doctor’s prescription, or over the counter medication intake.

At the beginning of the nineties second-line drugs, viewed as aggressive therapies, were increasingly prescribed for early RA subjects (20, 24). It can be noted that the practice in North America showed a different pattern which has been the subject of several publications. In the early eighties, the main second line treatments prescribed were gold salts and D-penicillamine. Then, in the nineties, hydroxychloroquine, sulfasalazine, azathioprine, and especially low-dose methotrexate became the major second-line drugs. Methotrexate was still in use for 50% of patients after 60 months (25, 26). In Europe, a study from Finland (7) about drug consumption in two cohorts of early RA, started in the 70’s and in the 80’s respectively, showed that second-line treatment use became more extensive over time, the later cohort having been more often treated with methotrexate.

NSAIDs, rather than corticoids, were found in association with second-line treatment. This attitude was comparable in all three countries. For a long time, NSAIDs were prescribed at the outset, before corticoids, since they had a better public image and were also viewed more favourably by the medical profession. But patterns of choice or association between NSAIDs and corticoids varied from one country to another.

The possible reasons for divergence in drug consumption and prescription are numerous: university teaching, care systems, pharmaceutical marketing strategies, etc. The impact of university teaching is difficult to measure. Care units attached to university settings with research and teaching units probably offer different care than non-university care units (27). Organisation and functioning of continuing education systems also differ. Continuing education for doctors has only recently become compulsory in France. Economic pressures over the last twenty years has led to modifications in the organisation of health care systems. At the time of the study in North European countries, the referral and care distribution varied (28). The private sector was particularly developed in France. Also, access to specialist practitioners was freer in France than in the Netherlands, where the general practitioner (GP) acted as a “gatekeeper”. Norway was in an intermediate situation in this respect. In Scandinavian countries, the specialists provide the regular follow-up for RA patients, while in France this role generally belongs to the GP. In most countries, the major part of medical costs, including drugs for chronic conditions (like RA), is covered by the state or the social security system, sometimes complemented by private insurance systems. At the time of the study in France, most of patients with RA were entitled to a 100% insurance coverage. In the other countries, there were fixed-rate systems (28).

With respect to pharmaceutical laboratories, economic potential varies between nations, because of variations in the way prices are fixed and in the procedures for authorising the drug marketing. In this area, considerable differences remain, despite the development of European procedures.

In conclusion, the data from this study document drug consumption in the first years of RA and can be used as a reference or as comparative data for benchmarking current and future drug consumption studies. A general survey on the nineties is in
progress, in order to confirm the changes in practice observed, and their degree of disparity in Europe given the changes in health care provision in the light of economic constraints.

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Drug consumption in RA in the 90’s in Europe