Direct Health Costs of Inflammatory Polyarthritis 10 Years after Disease Onset: Results from the Norfolk Arthritis Register

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ABSTRACT. ***Objectives***. To explore the change in direct medical costs associated with inflammatory polyarthritis (IP) 10 to 15 years after its onset.

Methods. Patients from the Norfolk Arthritis Register who had previously participated in a health economic study in 1999 were traced 10 years later and invited to participate in a further prospective questionnaire-based study. The study was designed to identify direct medical costs and changes in health status over a 6-month period using previously validated questionnaires as the primary source of data.

Results. A representative sample of 101 patients with IP from the 1999 cohort provided complete data over the 6-month period. The mean disease duration was 14 years (SD 2.1, median 13.6, interquartile range 12.6–15.4). The mean direct medical cost per patient over the 6-month period was £1496 for IP (inflated for 2013 prices). This compared with £582 (95% CI £355–£964) inflated to 2013 prices per patient with IP 10 years earlier in their disease. The increased cost was largely associated with the use of biologics in the rheumatoid arthritis subgroup of patients (51% of total costs incurred). Other direct cost components included primary care costs (11%), hospital outpatient (19%), day care (12%), and inpatient stay (4%).

Conclusion. The direct healthcare costs associated with IP have more than doubled with increasing disease duration, largely as a result of the use of biologics. The results showed a shift in the direct health costs from inpatient to outpatient service use. (J Rheumatol First Release April 1 2015; doi:10.3899/jrheum.140528)

Key Indexing Terms:
INFLAMMATORY POLYARTHRITIS
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Inflammatory polyarthritis (IP), of which rheumatoid arthritis (RA) is a subset, is a chronic and disabling condition with a lifelong course and considerable economic effect both on the affected individual and on society[1]. In 1992, the annual costs of RA in England were estimated to be £1.26 billion[2] with the direct costs (the use of primary and secondary care services and drug costs) accounting for 48% of the total, the remainder reflecting indirect health costs. Almost 20 years later, the estimated cost of RA in England has risen to about £8 billion a year (Department of Health drug costs 2011)[3].

Establishing the true cost associated with IP is complex because costs change over the time course of the disease with age, disease progression, and changing treatment strategies. Secular changes in disease severity, the earlier introduction

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of disease-modifying agents, and the use of targeted management regimes together with the increasing availability of biologic agents are all likely to have complex and competing effects on longterm costs[4].

In 1999, as part of a wider assessment of the costs of new-onset IP, we examined the costs of disease using a cohort of 133 consecutive patients from the Norfolk Arthritis Register (NOAR) recruited between 1994 and 1999[5]. Of this cohort, 50% subsequently developed RA. An analysis of the data obtained using a validated resource use and expenditure questionnaire[5,6] revealed that in the first 5 years after disease onset, direct health costs represented 14% of the total health service costs, the main component being inpatient and day care stays (33%). This was followed by prescribed medication, which accounted for 30% of the total health service costs.

In this followup cross-sectional study, we reevaluate the cost of the disease after a further 10 years in a sample taken from the same cohort of patients. This community-based longitudinal cohort design provides a unique opportunity to observe the changing costs of treatment associated with IP and its progression against a changing therapeutic backdrop.

MATERIALS AND METHODS

Study subjects. The NOAR is a longterm prospective cohort of over 4000 patients with new-onset IP (> 2 swollen joints lasting > 4 weeks) identified from primary care and hospital sources within the boundaries of the former Norwich Health Authority, UK, starting in 1990 and currently ongoing[7,8].

In 1999, a health economic evaluation was conducted prospectively over a 6-month period among 133 patients with IP in the community using self-completion postal questionnaires, designed and validated for the study[5]. These questionnaires (available from the authors on request) included detailed sections on primary care and hospital visits (to see doctors, nurses, or other healthcare professionals), prescribed medications, and over-the-counter drugs. An extra question was added to the original questionnaires under the medications section to identify the use of biologic disease-modifying antirheumatic drugs (DMARD) in the current study. Any reporting of biologic DMARD use was checked against the patients' paper records to ensure accurate recording of information. Questions on medications included the type of drugs used, dosage, number of prescriptions, and duration of treatment, enabling the calculation of costs using standard UK prices at individual patient level. A second cross-sectional study, which also took place in 1999, recruited 218 NOAR participants. Both studies in 1999 were designed to estimate the health service (direct health costs), non-health service (e.g., over-the-counter medications), and total costs of early IP[5]. The subjects recruited were consecutive patients entering NOAR between 1994 and 1999. When interviewed by the NOAR research nurses at the time of recruitment, 267 patients had given permission for further contact by the register and could be located in 2009. The remaining patients had died, declined NOAR in the intervening period, were untraceable, or had prearranged agreement with the study team in 1999 not to be contacted again.

Six-month prospective evaluation. All 267 eligible study subjects in 2009 were contacted by letter (with a reminder after 2 weeks if they had failed to respond) inviting them to participate in a 6-month prospective healthcare evaluation survey. A total of 141 consented to participate. Resource use and expenditure data were gathered at baseline (namely, at the start of our study), 3 months, and 6 months by self-completion of the same postal questionnaire used in 1999.

As in our previous study[5], study participants were provided with a memory aid in the form of a diary to record their resource use and expenditure over the 3-month followup intervals. Completion of the diary was optional and intended for the participants' personal use only.

The NOAR database holds information on sociodemographic data including age, sex, smoking status, social class, and ethnic group; social class was assigned using data from the Office of Population Censuses and Surveys, 1991[9], based on the occupation of the individual. Other clinical, laboratory, and radiographic data recorded in the NOAR database include the 28-joint Disease Activity Score (DAS28), Health Assessment Questionnaire (HAQ), C-reactive protein (CRP), rheumatoid factor and/or anticyclic citrullinated peptide antibodies, and presence of erosions on radiographs. Details on DMARD use were documented at each patient review.

Analytical approach (cost calculations). Unit costs were applied to the resource use data using data from the Personal Social Services Research Unit 2009, and for medications, the British National Formulary (BNF) 2009 was used[10]. Medications relating to IP treatment, including analgesics, DMARD, and bone-strengthening treatments, were costed individually using the BNF and based on the number of prescriptions, assuming that each prescription was for 1 month (from the data available). With regard to the biologics, only etanercept and adalimumab were prescribed in this study population. The BNF 2009 reports the price of both anti-tumor necrosis factors as £89.38 per 25-mg prefilled syringe for etanercept (standard dose of 25 mg twice weekly or 50 mg once weekly) and £357.50 per 40-mg prefilled syringe for adalimumab (standard dose 40 mg on alternate weeks).

The direct health costs per participant over 6 months were estimated following the same methodology as reported by Cooper, *et al*[5] in the earlier study. We combined resource use data with the unit costs using the following general costing formula[5]:

$$Total\ cost = \sum_{i=1}^{n} \sum_{j=1}^{m} (frequency)_{ij} \times (unit\ cost)_{j}$$

where i is the ith individual ($i = 1 \ldots n$) and j is the jth service received ($j = 1 \ldots m$; i.e., inpatient and outpatient care, and different second-line drugs).

All costs were inflated to 2013 prices (Bank of England inflation calculator)[11]. A table of unit costs where all costs are expressed in 2013 UK sterling is available from the authors on request.

Separate cost categories were then defined, including hospital, community, and treatment costs. Healthcare costs are typically right skewed[12] because of the small number of patients reporting high treatment costs compared with the population as a whole. For interpretation of our results, we report the following descriptive statistics for each variable:

1. Number and proportion (%) of participants using specific services.
2. Mean, SD, and the 95% CI for costs calculated on all resource use.

The individual costs per patient were calculated for the 6-month period using STATA 11 and Microsoft Excel.

RESULTS

Patient sample description. Of the 141 responders who consented to participate, 101 (72%) returned complete data at baseline, 3 months, and 6 months. Their baseline characteristics are shown in Table 1. Their mean age was 49.8 years (SD 12.0), 63% were women, and the mean disease duration was 14 years (SD 2.1, median 13.6, interquartile range 12.6–15.4). The baseline characteristics in our present study were broadly similar to the baseline characteristics of the subjects originally included in the 1999 study. The only difference was longer disease duration. The patients in the current study had comparable age at symptom onset with the 1999 cohort (mean 50 yrs vs 52 yrs, respectively), similar disease duration at entry (47 mos vs 51 mos), sex (female

Table 1. Patient characteristics by RA status at the time of recruitment into the study. Values are mean (SD) or median (IQR) unless otherwise specified.

Characteristic	IP, n = 101	RA Group*, n = 64
Age at symptom onset, yrs	49.8 (12.0)	51.1 (11.5)
Disease duration, yrs	14 (2.1)	14.4 (2.2)
Female, n (%)	64 (63)	49 (77)
HAQ score	0.63 (0.13–1.19)	0.88 (0.38–1.38)
DAS28-CRP	3.6 (1.4)	4.2 (1.1)
CRP, mg/l	7 (0–15)	11 (3–23)
SJC-28	3 (1–8)	5.5 (2–11)
TJC-28	4 (1–6)	5 (2–9)
RF-positive, n (%)	32 (34)	28 (45)
Anti-CCP–positive, n (%)	27 (31)	25 (44)
Erosions, yes, n (%)	10 (51)	9 (69)
On DMARD, n (%)	36 (36)	24 (38)

*Classified by the ACR criteria applied at 5 years after disease onset. RA: rheumatoid arthritis; IQR: interquartile range; IP: inflammatory polyarthritis; HAQ: Health Assessment Questionnaire; DAS28: 28-joint Disease Activity Score; CRP: C-reactive protein; SJC-28: swollen joint count at 28 joints; TJC-28: tender joint count at 28 joints; RF: rheumatoid factor; anti-CCP: anticyclic citrullinated peptide antibodies; DMARD: disease-modifying antirheumatic drugs; ACR: American College of Rheumatology.

64% vs 62%), and HAQ at entry (median 0.63 vs 0.75). Compared with the 1999 study, as would be expected with longer followup, a greater proportion of patients (63% compared with 50%) had been classified by the American College of Rheumatology criteria[13] as having RA. Biologic drugs were used by 14 patients (14%) during the 6-month study period. As expected, those who developed established RA during followup showed higher DAS28, CRP, and HAQ at baseline than the group overall.

Costs of disease. The total direct cost incurred by all patients with IP (n = 101) was £128,903 over the 6-month study period, with a mean cost of £1276 (95% CI £856–£1696, £1493 inflated for 2013 prices) per patient and a total annual direct (TAD) cost of £2556.00 (£2991, inflated for 2013 prices). Medications and biologic drugs accounted for the largest proportion of the total healthcare cost (54%), followed by hospital outpatient visits and day care admission (31%). Inpatient hospital stay for orthopedic intervention was required for 2 patients in the 6-month followup interval. Inpatient admissions accounted for 4% of the total cost in this sample. Outpatient hospital visits (including both consultations with doctors and nurses) accounted for 19% of the cost for IP, and use of day unit facilities accounted for 12%. Community visits, including visits to the general practitioner (GP), GP nurse and community physiotherapy, and occupational therapy accounted for 11% of the total cost of IP.

In those who developed RA (n = 64), the mean total cost per patient over the 6-month period was £1715 (95% CI £1105–£2326), TAD cost £3430 (£2007 and £4014, respectively, inflated for 2013 prices). Use of biologic drugs accounted for 51% of the total direct costs, despite only 14% of the cohort having been prescribed these drugs. Other IP-related medications accounted for an additional 6% of the cost.

The costs of all patients with IP and also the disaggregated costs for the RA group over the 6-month study period are reported in Table 2, displaying the 50th percentile (median), 75th, and 90th percentiles, and maximum values to allow for a clear representation of the distribution of the data.

DISCUSSION

The previous literature on the economic effect of IP and RA has focused on the short-term direct medical costs. This is the first study to identify the associated longterm direct medical costs in an era where emphasis is placed on the use of earlier and more intensive treatments. There has been a shift from a limited number of drugs with slow-acting and/or marginal effects to the use of more potent drugs, such as biologics when first-line synthetic DMARD fail to control disease. The clinical effectiveness and benefits of biologic agents on both short-term and longer-term outcomes of disease is now well established. However, they do represent the most expensive type of medication for IP and this restricts their use in the United Kingdom since their availability in 2002. Our study has shown that up to 15 years after the onset of IP, biologic agents accounted for over 50% of the total cost associated with disease.

However, like-for-like comparison with our earlier 1999 study for individual resource use is not possible because of methodological differences, individual cost components being grouped differently, and the focus of the study being on both direct and indirect costs. The 1999 study was not designed with longterm followup of health economic outcomes in mind, and a group of patients had a pre-arranged agreement not to be contacted further. While the present and original cohorts were broadly similar in their baseline characteristics, the possibility of selective difference influencing the comparison cannot be excluded fully. Nevertheless, we believe valid comparisons of broad trends for the most notable differences over time are possible. In the 1999 study, a greater proportion of the total 6-month health service costs (42%) were attributable to a minority of individuals who incurred an inpatient stay or day care visit (6%). These "high cost" individuals represented 10% of the cohort and incurred 50% of the total 6-month costs (both health and non-health services).

In the current study, outpatient visits and day care admission accounted for just under one-third of the cost (31%), whereas inpatient admission was only reflected by 4% of the cost over the 6-month period. The inpatient admissions were for orthopedic-related interventions. The observed shift from inpatient to outpatient care could be because of better management and more intensive treatment of patients in the outpatient setting and could relate to the use of biologic agents. However, we can only speculate on this observation, which could also simply be a reflection of the changing

Table 2. Disaggregated costs for IP and the RA subgroup. All costs are reported in £ sterling and for the price year of 2013. In view of the short study period of two 3-month intervals, mean resource use per patient was mostly once.

Resource Use	IP, n = 101		RA Group, n = 64	
	n (%)	Cost, £ 50th PL, 75th PL, 90th PL, max	n (%)	Cost, £ 50th PL, 75th PL, 90th PL, max
GP nurse visits	55 (54)	33, 169, 237, 950	43 (67)	84, 203, 237, 950
GP nurse calls	14 (14)	0, 0, 12, 77	10 (16)	0, 0, 21, 77
NP visits	40 (40)	0, 50, 150, 754	34 (53)	50, 100, 201, 754
NP calls	16 (16)	0, 0, 12, 38	13 (20)	0, 0, 21, 38
GP visit	47 (46)	0, 72, 145, 544	33 (52)	36, 72, 108, 544
GP call	15 (15)	0, 0, 44, 400	11 (17)	0, 0, 44, 400
Hospital doctor visits	56 (55)	143, 294, 442, 1917	41 (64)	147, 294, 442, 884
Hospital doctor calls	13 (13)	0, 0, 22, 333	11 (17)	0, 0, 22, 333
Day care stay	9 (9)	0, 0, 0, 5227	7 (11)	0, 0, 522, 5227
Inpatient stay	2 (2)	0, 0, 0, 3073	2 (3)	0, 0, 0, 3073
Physiotherapy	16 (16)	0, 0, 63, 252	10 (16)	0, 0, 63, 126
Occupational therapy	13 (13)	0, 0, 31, 126	11 (17)	0, 0, 53, 126
Total medication use	81 (80)	30, 103, 349, 845	56 (88)	39, 121, 356, 845
Total cost biologics	14 (14)	0, 0, 5021, 5021	13 (20)	0, 0, 5021, 5021

IP: inflammatory polyarthritis; RA: rheumatoid arthritis; 50th PL: 50th percentile (median); 75th PL: 75th percentile; 90th PL: 90th percentile; max: maximum value; GP: general practitioner; NP: nurse practitioner.

approach to delivering care to patients with IP in the United Kingdom.

The mean direct (health service) medical cost per patient over the 6-month period in our study was £1496 for all IP (inflated for 2013 prices). This compared with £582 (95% CI £355–£964), inflated to 2013 prices (£385, 95% CI £235–£638 in 1999 prices), per patient with IP 10 years earlier in their disease[5]. There has, therefore, been an obvious increase in costs, with the use of biologics being a major contributor.

While direct comparisons between studies based on differing healthcare systems using different economic evaluations is not possible, it is of interest that our figures are comparable to those reported in studies from the United States, Canada, and Europe, accounting for inflation[14,15]. In a prospective longitudinal study of costs incurred by patients with RA in Saskatoon, Saskatchewan and Montreal, Quebec, Canada[14], annual direct costs increased by almost 20% in the late 1980s compared to the early 1990s. Institutional stays and medications made up at least 80% of total direct costs, the former being more frequent in the older and more disabled, as one would expect. In the study that was published in 1997, the authors concluded that measures to reduce longterm disability by using earlier and more aggressive intervention have the potential to produce considerable cost savings. However, it was unknown then which strategies would have the greatest effect on outcome and the optimal allocation of resources. Direct comparison of the results with other studies can be challenging and may be inappropriate because of the differences in health systems, population characteristics (e.g., age, sex, disease severity, and duration)[1], as well as methodological differences (e.g., different cost components, unit costs, etc.). Therefore, the generalization of the results to a wider geographical area and other healthcare systems is not possible and is an unavoidable limitation of our study.

Our study is limited because information on the indirect healthcare costs (such as productivity losses to the individual, family, employer, and society as a result of illness) was not sufficiently and robustly collected, and we anticipate that our results will have underestimated the full societal cost of the disease. Details on investigational costs (e.g., for imaging and blood tests) were not included, which could result in the underestimation of costs. However, our aim was to provide a description of the direct medical costs in this cohort of patients with a view to assessing the changing cost of disease and healthcare use over time. By adopting similar methodology to our earlier study, we provide an overall assessment of their inpatient and outpatient care. Finally, the use of self-reported questionnaires to collect information on resource use, drug use, and costs is a limitation of the study. However, we minimized the risk of patient recall bias by providing study participants with a memory aid in the form of a diary to record their resource use and expenditure over the two 3-month followup intervals.

One of the key issues surrounding the use of biologic agents in IP is whether the longterm cost of the disease will be reduced by the introduction of more effective treatments earlier in the disease. Comparative data will be needed from later cohorts to provide insight into this. However, our study has shown that biologic use among this cohort currently dominates the direct cost of the longterm management of

IP when compared to all other aspects of direct medical care.

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