Health Economic Consequences of a Tightly Controlled Dose Reduction Strategy for Adalimumab, Etanercept and Ustekinumab Compared with Standard Psoriasis Care: A Cost-utility Analysis of the CONDOR Study

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A dose reduction strategy for adalimumab, etanercept and ustekinumab in patients with psoriasis who have stable and low disease activity has recently been compared with usual care in the CONDOR study (CONtrolled DOse Reduction) of biologics in patients with psoriasis with low disease activity. The aim of the current study was to perform a cost-utility analysis with a 12-month time horizon alongside this trial, using prospectively measured healthcare costs and quality-adjusted life years, based on Short-Form Six-Dimension utilities. Bootstrap analyses were used to calculate the decremental cost-utility ratio and the incremental net monetary benefit. The dose reduction strategy resulted in a mean cost saving of €3,820 (95th percentile −€3,099 to −€4,509) per patient over a period of 12 months. There was an 83% chance that dose reduction would result in a reduction in quality adjusted life years (mean −0.02 (95th percentile −0.06 to 0.02). In conclusion, dose reduction of biologics resulted in substantial cost savings with an acceptable reduction in quality of life.

Key words: psoriasis; biologics; CONDOR study; cost-utility; dose reduction strategy.

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SIGNIFICANCE

Psoriasis is a chronic inflammatory skin disease with a substantial impact on patients and on healthcare expenditure. This study evaluated the cost-effectiveness of a dose reduction strategy for adalimumab, etanercept and ustekinumab vs standard care over a 12-month period in patients with psoriasis in the Netherlands. Analysis showed that this dose reduction strategy resulted in relevant cost savings with a minimal decrease in quality adjusted life years.

Psoriasis is a chronic immune-mediate inflammatory skin disease for which several targeted biologic therapies are available. These drugs have dramatically improved the lives of patients with psoriasis: low disease activity has become a realistic goal (1–3). The biologics adalimumab, etanercept and ustekinumab are frequently used. However, chronic use of these biologics has a high impact on healthcare expenditure (1, 4). The approximate costs per patient per year are between €15,000 and €27,000 (5), although the introduction of biosimilars will reduce these costs. Moreover, the use of biologics can be associated with side-effects, such as increased risk of infections and non-melanoma skin cancer (6–9). Therefore, aiming for the lowest effective dose and improved efficiency of use of these biologics is desirable.

Previous research has shown that dose reduction or interval prolongation in patients with psoriasis might lead to lower cumulative exposure and cost savings, without deterioration in disease activity (10–15). We recently published the initial results of a pragmatic randomized trial comparing a tightly controlled dose reduction strategy for adalimumab, etanercept and ustekinumab for psoriasis with usual care; the CONDOR study (16). The dose of biologics was reduced in small steps, while intensively monitoring disease activity. It was not possible to prove non-inferiority regarding the primary outcome; Psoriasis Area and Severity Index (PASI), with a PASI difference of 1.2 (95% confidence interval (95% CI) 0.7–1.8) points after one year between dose reduction and usual care. The study demonstrated non-inferiority with regard to the main secondary outcome; Dermatology Life Quality Index (DLQI) (16). In addition, dose reduction was successful in 53% of patients with psoriasis, and no difference was seen in persistent disease flares between dose reduction and usual care groups (16).

Economic evaluation would provide additional evidence on which base the decision whether to implement a dose reduction strategy in daily practice. Although prolonging the interval of the biologic will save medication costs, this strategy may also increase the patient consultations and therefore increase healthcare costs. In addition, possible disease flares after dose reduction

could decrease health-related quality of life (QoL). On the other hand, such a dose reduction strategy might be considered a cost-effective intervention when reduction in QoL is compensated by large cost savings. Indeed, similar dose optimization strategies in rheumatoid arthritis (RA) have been shown to be cost-effective on the short- and long-term (17–19). Therefore, an economic evaluation is mandatory, comparing a tightly controlled dose reduction strategy with usual care and relating differences in costs to differences in quality adjusted life years (QALYs).

METHODS

Study design and participants

This economic evaluation was a pre-planned piggy-back analysis of the CONDOR study (CONtrolled DOse Reduction) of biologics in patients with psoriasis with low disease activity (16). Hence all necessary data were collected alongside the clinical trial. The CONDOR study was a pragmatic, open-label, randomized, non-inferiority (NI) trial for adalimumab, etanercept and ustekinumab, comparing a dose reduction strategy with usual care in patients with psoriasis and low disease activity. The rationale, design, and outcomes have been comprehensively described and summarized previously (16, 20). Patients with plaque psoriasis were eligible for dose reduction when they had stable and low disease activity using the authorized full dose of adalimumab, etanercept or ustekinumab for at least 6 months. Plaque psoriasis was always the main indication for the biologic, but other phenotypes could co-exist. Stable low disease activity was defined as PASI score ≤ 5 at 2 subsequent visits in the last 6 months, and a Dermatology Quality of Life Index (DLQI) score ≤ 5 at study inclusion. The CONDOR study was performed in one academic and 5 regional hospitals from March 2016 through July 2018 and approved by the local ethics committee (Commissie Mensgebonden Onderzoek region Arnhem-Nijmegen, NL54557.091.15). The study was performed in a period when biosimilars were not available for these biologics. The CONDOR trial and this pre-planned economic evaluation were registered at ClinicalTrials.gov (NCT 02602925) and performed according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients prior to participation.

Trial procedures

Patients were randomly assigned (1:1) to the dose reduction or usual care group. Patients randomized to the usual care group continued their standard full dose of adalimumab, etanercept or ustekinumab. Patients were seen every 3 months, decisions regarding dose tapering were made at the scheduled visits, and patients were encouraged to contact their physician when experiencing increased symptoms of disease activity. Patients allocated to the dose reduction group received identical care to that of the usual care group, but the time between injections was prolonged in 2 steps. This led to 66% and 50% of their original dose, through administration of adalimumab every 21 and 28 days, etanercept every 10 and 14 days and ustekinumab every 18 and 24 weeks, respectively. In case of a disease flare patients returned to their previous effective or original dose. A flare was defined as a PASI score > 5 and/or a DLQI score > 5 at one visit. No further attempts at dose reduction were made after a flare. Patients were allowed to continue or start methotrexate/acitretin, or use topical therapies, during the study.

Utilities

This cost-utility analysis measured generic health-related QoL with the Short Form Health Survey (SF-36) (21). Utilities were calculated based on the 12 specific SF-36 questionnaire answers included in the SF6D system. Although the EuroQol 5 Dimensions (EQ5D) system is the most used system to measure utilities for economic evaluations, when designing the study it was considered that the SF6D showed better face validity for patients with psoriasis. It was expected, therefore, that we would be better able to detect small differences in QoL between the 2 groups, especially as the study population consisted of patients with low disease activity and good QoL, as this was an inclusion criterion. Furthermore, the SF6D system is recommended by the Dutch guideline for economic evaluation as an alternative for the EQ5D (22). Missing values in utility scores were linearly interpolated between time points and on a patient level. This data was used to calculate the area under the curve, representing QALYs per patient.

Costs

Costs were determined mainly from a medical perspective. Volumes of care were registered using standardized case record forms and collected using electronic patient records. The study focused on psoriasis care: psoriasis medication used, outpatient visits or telephone contacts with dermatologists and rheumatologists (an increase might result from the advice in the dose reduction group to tightly control disease activity), and hospital admissions related to psoriasis flares. Because of the expected increase in outpatient visits travel expenses were included; the travel distance for each patient was set at 7 km, which is the mean travel distance to a hospital in the Netherlands (23, 24). All data on biologic use were specifically queried and recorded, and the cumulative biologic medication use was calculated per patient. Topical therapy or methotrexate/acitretin used was registered, but not incorporated in the cost analysis due to the marginal effect on total costs compared with biologics.

The healthcare cost prices were based on the Dutch Guideline for Cost Analyses (23, 24). The medication prices were obtained from the Dutch national tariff list (5). The details of the prices that were used for this manuscript can be found in Table SI[1]. All prices were converted to 2018 levels using the general Dutch price index rate. No discounting on costs was needed, due to the 12-month follow-up duration of the CONDOR trial on which this economic evaluation was based. In addition, in order to anticipate possible lower drug prices in the future, sensitivity analyses were performed with 30%, 50% and 80% reductions in costs of medication.

Statistical analysis

Descriptive statistics were used for baseline characteristics, co-medication and healthcare usage and compared for usual care vs dose reduction. Depending on the skewness of the data, means and standard deviations (SD)/95% confidence interval (95% CI) or medians with interquartile ranges (IQR) for continuous variables and proportions for nominal variables were given. The proportion of patients who successfully tapered their dose was calculated. Successful dose tapering was defined as patients with a lower biologic dose than normal while maintaining PASI and DLQI scores ≤ 5. Proportions of patients with topical therapy, methotrexate and acitretin use were compared between groups, using a Fisher's exact test. The number of consultations (outpatient visits) and telephone contacts were also compared between groups using

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an independent *t*-test or a non-parametric alternative in case of a skewed distribution (Mann–Whitney *U* test). The mean cumulative biologic dose per patient, for each biologic throughout the study, was calculated. The percentage of the dose used in dose reduction relative to usual care was calculated.

Cost-utility analysis

The cost-utility analysis was based on an intention-to-treat analysis. A possible small, but acceptable, reduction in QALYs was anticipated, and therefore incorporated in the pre-planned analysis by determining a decremental cost-utility ratio (DCUR): dividing the difference in costs by the difference in QALYs between both groups. The DCUR represents by how much financial gain a loss of one QALY will be compensated. The 95% uncertainty boundaries in DCUR were calculated using bootstrapping with 1,000 replications, which are plotted in a cost-utility plane. The incremental net monetary benefit (iNMB) per patient was calculated for varying levels of willingness to accept (WTA), in Euros per QALY lost, using the formula: (WTA*incremental QALYs) – incremental costs. This results in the net amount of money saved, when the possible reduction in QALY is compensated by the amount society needs to gain in order to accept a reduction in QALY (the WTA) (25). In the studied population, the disease burden was low because of their state of low disease activity; in the Netherlands, in such cases a willingness to pay (WTP) value of €50,000 is generally used. However, it is conceivable that one would want a reduction in QALY to be compensated by higher amounts than one is willing to pay to gain a QALY; hence, WTA levels often exceed WTP levels. Therefore, a more conservative approach was chosen, and a WTA of €80,000 was used, which is the amount of money that Dutch society is maximally willing to pay for a QALY gained.

RESULTS

Patients

In total, 120 patients were included; 60 in the dose reduction group and 60 in the usual care group (16). Baseline characteristics are shown in **Table I**. Two patients were lost to follow-up and 2 other patients had too few SF-36 utility values to calculate a QALY, leaving 58 patients in the dose reduction group and 58 patients in the usual care group for the intention-to-treat analysis. One patient was lost to follow-up due to psychiatric illness, and the treatment of the other patient was continued in a non-participating hospital. Baseline characteristics were well balanced between the dose reduction and usual care groups (Table I). These characteristics mimic an average biological psoriasis cohort, except for the low disease activity at baseline due to the inclusion criteria of the CONDOR. Limited data were missing: 1% of the planned visits, 1% of PASI, 2% of DLQI, and 6% of SF-36 measurements.

Healthcare usage

At 12 months, 28 patients (53% (28/53), 95% confidence interval (95% CI) 39–67%) in the dose reduction group tapered their dose successfully. Ten patients (19% (10/53), 95% CI 10–32%) used two-third of their original dose and 18 patients (34% (18/53), 95% CI 22–48%) used half of their original dose. The mean cumulative dose per patient, for each biological throughout the study was calculated and compared between the dose reduction group and usual care group. The percentage cumulative dose reduction was 34% in the adalimumab group, 26% in the etanercept group, and 23%/34% in the ustekinumab (45 mg/90 mg) group, respectively (16).

Concerning co-medication at baseline, 7% of patients used methotrexate or acitretin in both the dose reduction group and usual care group. No patients started treatment with methotrexate or acitretin during the study. Patients who were on this co-medication at the start of the study continued its use during the study. A significant difference was seen between dose reduction and usual care regarding use of topical corticosteroids. In the dose reduction group, 73% (44/60) (95% CI 60–84%) of patients used topical steroids with a mean of 87 days (95% CI 65–109 days) during the study period of 12 months. For the usual care group, 35% (21/60) (95% CI 23–48%) used topical steroids with a mean of 35 (95% CI 20–50) days ($p < 0.001$, Fisher's exact test).

Regarding other healthcare usage, there were slightly more consultations in the dose reduction group (median 5.0 (IQR 1.0) per patient) compared with the usual care group (median 5.0 (IQR 0.0) per patient) ($p = 0.018$) for 12 months. There were also more telephone contacts with patients in the dose reduction group (median 0.0; IQR 1.0) contacts per patient) compared with the usual

Table I. Baseline characteristics

Patient characteristics	Usual care ($n = 60$)	Dose reduction ($n = 60$)
Male, *n* (%)	42 (70)	40 (67)
Age, years, mean ± SD	57 ± 13.3	53 ± 12.9
Onset psoriasis, years, mean ± SD	28 ± 14.0	24 ± 11.4
Disease duration, years, mean ± SD	28 ± 12.3	28 ± 12.9
Biologic duration, years, mean ± SD	4.8 ± 2.9	4.0 ± 2.8
Psoriatic arthritis, yes, *n* (%)	12 (20)	19 (32)
Body mass index (kg/m^2), mean ± SD	28 ± 4.9	29 ± 5.4
Disease activity		
PASI, median [IQR]	1.3 [0.3–2.7]	1.8 [0.6–2.8]
DLQI, median [IQR]	0.0 [0–2]	0.0 [0–1]
C-reactive protein, mean ± SD	2.8 ± 5.3	2.2 ± 2.0
Medical history, *n* (%)		
Diabetes mellitus (1–2)	10 (17)	7 (12)
Hypertension	23 (38)	20 (33)
Hypercholesterolaemia	20 (33)	16 (27)
Myocardial infarction	4 (7)	3 (5)
Cerebrovascular incident	4 (7)	4 (7)
Malignancy	5 (8)	2 (3)
NMSC	5 (8)	2 (3)
IBD	1 (2)	0 (0)
Rheumatological condition	11 (18)	10 (17)
Number of previous biologics	31 (52)	30 (50)
Treatment in the study, *n* (%)		
Adalimumab	27 (45)	25 (42)
Etanercept	14 (23)	14 (23)
Ustekinumab	19 (32)	21 (35)
Concomitant methotrexate/acitretin	4 (7)	4 (7)

SD: standard deviation; IQR: interquartile range; PASI: Psoriasis Area and Severity Index; DLQI: Dermatology Life Quality Index; NMSC: non-melanoma skin cancer; IBD: inflammatory bowel disease. No data on baseline characteristics were missing.

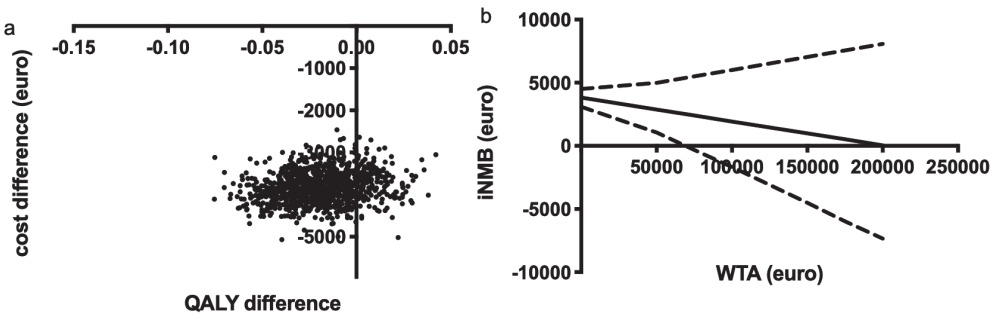

Fig. 1. Cost-utility plane and cost-utility acceptability curve. (a) Results of costs and utility estimations in cost-effectiveness (CE) plane, based on 1,000 bootstrapped replications. (b) Cost-effectiveness acceptability. iNBM: incremental net monetary benefit; WTA: willingness to accept; QALY: quality-adjusted life year.

care group (median 0.0; IQR 0.0) contacts per patient) ($p = 0.001$).

Cost-utility

In **Fig. 1**a and **Table II**, the results of 1,000 bootstrapped replications concerning mean QALYs and costs for the 12 months study period are presented. Table SII[1] shows the mean costs per group (dose reduction vs usual care). The dose reduction strategy resulted in a mean QALY loss of –0.02 QALY (95th percentile –0.06 to 0.02). The chance of a reduction in QALY was 83%. All replications showed cost savings, with a mean of –€3,820 (95th percentile –€3,099 to –€4,509). The mean DCUR was €95,889 (95th percentile €1,687,233 to dominant) of savings per QALY lost. In Fig. 1b the iNMB of the dose reduction group is presented for varying WTA values. When a WTA level of €80,000 per QALY is chosen, the mean iNMB is €2,311 (95th percentile –€590 to €5,595) per patient in 12 months. With the WTA of €80,000, in 94% of the replications there is still a positive iNMB.

Sensitivity analyses for 30%, 50% and 80% lower prices for biologic drugs were also performed. The mean cost savings with 30% lower prices for biologics was –€2,633 (95th percentile –€2,111 to –€3,119), with 50% lower prices –€1,849 (95th percentile –€1,473 to –€2,222) and with 80% lower prices –€661 (95th percentile –€485 to –€818). Furthermore, in case of 30% lower drug prices, the mean iNMB with WTA of 80,000 per QALY would be €1,181 (95th percentile –€1,793 to €4,068), in case of 50% drug reduction, the mean iNMB would be €439 (95th percentile –€2,512 to €3,359) per patient and in case of 80% drug reduction, the mean iNMB would be –€803 (95% percentile –€3,999 to €2,284) (**Fig. 2**).

DISCUSSION

This cost-utility analysis alongside the CONDOR study, a pragmatic, randomized controlled non-inferiority trial (16), shows that a dose reduction strategy for the biologics adalimumab, etanercept and ustekinumab for patients with psoriasis would result in substantial cost savings (mean –€3,820 per patient over 12 months (95th percentile –€3,099 to –€4,509)). Also we found a probable chance (83%) of a small reduction in QALY. Although it is likely that a dose reduction strategy would result in a reduction in QALY, this loss was small and not statistically different from zero (mean QALY difference of – 0.02 (95th percentile –0.06 to 0.02)). When this decrease in QALY is compensated by the amount society wants to gain in order to accept a QALY loss, the net amount of money saved is still substantial.

To the best of our knowledge, this is the first prospectively performed economic evaluation of a tightly controlled dose reduction strategy for biologics in patients with psoriasis compared with usual care. Several studies have been performed on dose reduction, but no randomized prospective studies have been performed and economic analyses were lacking. In the original publication of the CONDOR trial we described that, based on the PASI, non-inferiority was not demonstrated for the dose reduction group compared with usual care with the chosen non-inferiority margin (16). However, the strategy was non-inferior based on the DLQI, and dose tapering did not result in persistent flares or safety issues. In this paper we show considerable cost savings, which could be an important driver for implementation, and highlights the importance of this study (10–12, 14).

The strength of the CONDOR study was its high internal validity by means of randomized design, the use

Table II. Mean quality adjusted life years (QALY) and costs for both groups

	QALY Mean (range)	Incremental QALY Mean (range)	Costs Mean (range)	Incremental costs Mean (range)
Usual care	0.83 (0.80;0.85)		€14,071 (13,503;14,559)	
Dose reduction	0.81 (0.78;0.84)	–0.02 (–0.06;0.02)	€10,251 (9,814;10,742)	–€3,820 (–3,099;–4,509)

Data are presented as means with 95th percentile as a result of 1,000 bootstrapped replications.

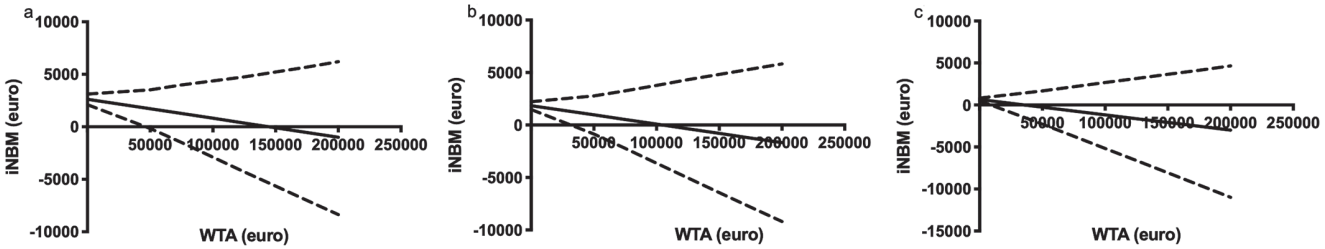

Fig. 2. Cost effectiveness acceptability curves for lower drug prices. (a) Analysis with 30% lower drug prices. (b) Analysis with 50% lower drug prices. (c) Analysis with 80% lower drug prices. iNBM: incremental net monetary benefit; WTA: willingness to accept.

of validated outcome measures and good data integrity. Furthermore, this economic evaluation alongside the CONDOR trial benefits from the pragmatic design of the original trial in terms of no blinding, no strict inclusion and exclusion criteria, permission for use of other anti-psoriatic drugs, and therefore it mimics daily practice. The last point is especially important for the generalization of an economic evaluation for use in deciding whether to implement a new strategy in daily practice.

Study limitations

A limitation of this study was the open-label design, which might have introduced reporting bias. In this economic evaluation this might have led to reporting more flares or worse QoL, especially in the dose reduction arm. However, if this were the case, a lower difference would have been found between both treatment arms than the true difference, which, in the current study, is a conservative estimation. Furthermore, this economic evaluation was based on a relatively short follow-up period of 12 months, which could therefore be considered as a limitation. Some effects related to dose reduction may not be seen in this time window and therefore cannot be evaluated. For example, lower cumulative doses of biologics could potentially lower long-term risks, such as cancer, and thereby potentially increase health-related cost-savings in the future (6). However, this is also true for the negative effects of withdrawing biologics, such as the long-term effects of the increase in topical corticosteroid use or reduction in their possible protective effect on cardiovascular disease (26). In addition, the costs related to work productivity were not included. However, absenteeism due to stable psoriasis is scarce, and therefore it was decided to include only healthcare-related costs measured from a medical perspective (27). Although productivity losses due to flares are possible, the CONDOR study demonstrated no significant difference in persistent flares between the groups (16). Hence we expect no influence on the incremental costs. In addition, the choice of SF6D utilities instead of EQ-5D utilities, which is the most often used instrument in economic evaluations, might be considered a limitation. There are no validation studies showing the responsiveness of either instrument in a psoriasis population with stable low disease activity. Therefore SF6D was used, because it was considered that the SF6D items were more relevant for psoriasis than the EQ-5D items. In view of the early detection of disease flares within the context of dose reduction, SF6D was considered more appropriate than EQ-5D. Mapping of DLQI items to EQ5D utilities is also presented in the dermatological literature; however, this is an indirect way of estimating utilities, and is therefore not recommended by pharmaco-economic guidelines. Cost-effectiveness could not be calculated according to individual drugs; however, the results of this cost-effectiveness analysis were not driven by a single drug, as the dose reduction percentages were in the same range for all 3 drugs.

Lastly, another limitation of this study could be the generalizability of the results to other countries. In addition to general differences in healthcare systems, and hence healthcare-related costs, the implementation of a dose reduction strategy could be different in other countries compared with the Netherlands (28, 29). However, we consider that cost savings in biologics, achieved through a dose reduction strategy, will always negate the cost savings of the implementation of this strategy. Because the medication costs are the main cost-driver, we advise comparing the drug prices between countries in order to estimate the potential cost savings in the country of use. To gain insight into the influence of varying drug prices on the conclusion of this study, a sensitivity analysis was performed, with 30%, 50% and 80% reductions in the cost of biologics. In conclusion, cost savings will be lower with higher discount percentages, but the mean cost savings and iNMB remained positive up to an amount of €100,000 as compensation for a reduction in QALY and 50% reduction in drug prices. However, with an 80% reduction in drug costs there is a substantial chance that the iNMB will be negative, meaning that dose reduction will increase the costs when compensated by a reduction in QALY with any WTA.

Another important factor that needs to be considered is that the WTA level is important in the generalizability of the presented results. With a lower WTA level the incremental net monetary benefit will be higher. Finally, policymakers and society must decide what society is willing to pay or accept.

We would like to stress that, in order to gain similar results in terms of cost savings, one needs to implement

the dose reduction strategy including a tightly controlled setting. Tightly controlled monitoring can contribute to earlier identification of disease flares, which can lead to prevention of under-treatment in these patients and minimization of the reduction in QoL. Tight control could mean that the workload of the treating physician increases; the current study found modest increases in telephone contacts and outpatient visits. Altogether, this potential increase in workload will be outbalanced by significant cost savings. We expect that this increase in workload is an effect that occurs particularly in the first year of dose reduction. In subsequent years, patients are expected to reach a stable dose, minimizing the number of extra visits needed. This expectation is confirmed by the cost-effectiveness analysis of dose-reduction strategy studies performed in rheumatoid arthritis (17–19).

Another implication related to dose reduction that must be considered is that the use of co-medication might be increased, as seen with regard to the use of topical corticosteroids. In the dose reduction group 73% of patients used topical corticosteroids vs 35% in usual care during the follow-up time of one year. It has been shown recently that the application of topical treatments has a detrimental effect on QoL, which increases with the duration and frequency of applications (30). This may be part of the explanation for the slight reduction in QALY in the dose reduction group in the current study. For future dose reduction studies a measurement tool should be used to capture this aspect, such as the Patient Benefit Index or a treatment satisfaction questionnaire.

Conclusion

A tightly-controlled dose reduction strategy in patients with psoriasis treated with adalimumab, etanercept or ustekinumab results in substantial cost savings and a minimal reduction in QALYs. Therefore, in psoriasis treatment, the implementation of a dose reduction strategy combined with tight control of disease activity will reduce the budget impact of the use of biologic therapies.

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Data-sharing statement: All legally and ethically permitted data will be shared on reasonable request if this is permitted by Dutch law.

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