Treatment Outcomes in Refractory Lupus Nephritis: Data From an Observational Study

Subodh Gururani (subodh.aqua@gmail.com)
Nizam's Institute of Medical Sciences https://orcid.org/0000-0002-7163-7557
Phani Kumar Devarasetti
Nizam's Institute of Medical Sciences
Megha Uppin
Nizam's Institute of Medical Sciences
Liza Rajasekhar
Nizam's Institute of Medical Sciences

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Abstract

Objectives

Despite current advances in treatment, refractory lupus nephritis (RLN) continues to pose a challenge. The present paper studies the clinical profile and treatment outcomes in patients with RLN.

Methods

This was an observational, bidirectional study enrolling consecutive patients of lupus nephritis from August 2018 to January 2019, who either failed to improve within three months, did not achieve partial renal response (PR) at six months, or did not achieve complete renal response (CR) after two years of treatment. Patients were followed every three months; treatment details and outcomes [CR, PR, no renal response (NR)], doubling serum creatinine, and death were recorded. Group comparisons were made using ANOVA and chi-square test. Factors affecting renal response were studied using linear regression.

Results

Forty-five of forty-eight enrolled patients completed at least nine months of follow-up and were included in outcome analysis. The median (IQR) SLE duration was three years (2–6 years). The majority of patients (n = 25) had proliferative lupus nephritis (LN) (ISN/RPS class III/IV), with nine patients having pure membranous LN (class V). The mean (SD) activity and chronicity indices were 8 (3) and 0. Over a median (IQR) follow-up period of 15 (12–27) months, 28 had CR, 9 had PR, and 8 showed no response to a switch in an immunosuppressive agent. Repeat renal biopsy (n = 8) with a mean (± SD) biopsy interval of 2 (± 1) years showed histological class transformation in more than half of the patients. There was no significant difference in treatment outcome and time to attain response based on individual immunosuppressive (IS) agent or sequence of IS agents used. None of the variables (duration of SLE or nephritis, baseline SLEDAI, leukopenia, hypertension, elevated anti-dsDNA, low complements, serum albumin, 24-hour urinary protein, biopsy class) predicted renal response on univariate analysis. No patient had a doubling of serum creatinine or progression to end-stage renal disease. There were three deaths, all related to infection.

Conclusion

The present study shows that a change in immunosuppression produces response in most RLN patients while a fifth of them showed no response to therapy. No predictor of renal response was identified. Histologic class switch was frequent. Renal function did not decline over a year of follow-up. Mortality was the direct cause of infection.

Key Messages

- A complete response following a switch in immunosuppression occurs in a significant proportion of patients with RLN.
- No response after switching the IS agent is seen in a significant minority.
- Histologic class switch often occurs over time.

Introduction

Lupus nephritis (LN) is present in about one-third of systemic lupus erythematosus patients at diagnosis and up to two-thirds during the disease course [1]–[3]. Progression to end-stage renal disease (ESRD) is a dreaded outcome. Even though the use of newer agents in the treatment, between 20%-70% of patients with LN, do not respond to initial immunosuppressive (IS) therapy [4]–[6]. Non-responders have poor survival, including renal survival at ten years compared to complete or partial responders [7]. In epidemiologic studies, poor prognostic factors reported for LN include hypertension, hypocomplementemia, anti-dsDNA antibodies, high serum creatinine and nephrotic syndrome at initial presentation, and low hematocrit as well as failure to achieve clinical remission within the first year of treatment [8]. Higher NIH activity index (AI) and chronicity index (CI) scores on renal histology are associated with doubling serum creatinine, end-stage renal disease, or death [9]. Treatment non-compliance, class VI LN, thrombotic microangiopathy, antiphospholipid syndrome, or lupus podocytopathy are other causes of persistent renal dysfunction to be considered before labeling as refractory LN (RLN) [10].

ACR defines an inadequate response to the first-line treatment in LN as disease worsening at three months or treatment failure by six months [11]. EULAR/EDTA labels patients who fail to improve within 3-4 months, or do not achieve partial response after 6-12 months, or complete response after two years of treatment, as having refractory disease [12]. The ACR definition leads to an earlier declaration of RLN since assessment is done at 3-6 months, while in EULAR-EDTA criteria, it could be done up to 12 months.

There is paucity of literature capturing outcomes after change in therapy in non-responders to first line therapy for lupus nephritis. Since it is not easy to conduct a randomised controlled trial in this group of patients, we believe that this study presenting such data in 48 patients followed prospectively with well documented details of therapy and outcome, will contribute to evidence which will guide therapy in initial non-responders. This study aims to assess the clinical profile and treatment outcomes in patients with LN resistant to first-line drugs. Documenting the response to a switch to an alternate immunosuppressive (IS) agent will shed light on whether refractoriness in LN is due to the patient or drug-related factors.

Methods

This was an observational, longitudinal, bidirectional study. Consecutive patients fulfilling the classification criteria of SLE based on Systemic lupus international collaborating clinic criteria (SLICC)

2012 [13], attending the Rheumatology Department at Nizam's Institute of Medical Sciences, Hyderabad, and satisfying the EULAR/EDTA definition of RLN, were enrolled in the study between August 2018 and January 2019. Patients with overlap connective tissue diseases, irregular follow-up, or non-compliance to therapy were excluded. Each patient was followed for at least nine months after enrollment.

Lupus nephritis was defined as per ACR criteria [14]. Complete renal response (CR) was defined as spot UPCR <50 mg/mmol (equivalent to proteinuria <0.5 g/24 h) and normal or near-normal (within 10% of normal GFR, if previously abnormal) GFR. Partial renal response (PR) was a ≥50% reduction in proteinuria to sub-nephrotic levels and normal or near-normal GFR. Lack of improvement, i.e., no reduction in proteinuria or deterioration of GFR, was defined as no renal response (NR). RLN was defined according to EULAR/ERA-EDTA recommendations as NR at three months, failure to achieve either PR at six months or CR after two years of treatment following induction treatment [12].

Demographic, clinical, and laboratory parameters (complete blood count, anti-dsDNA antibody and complement levels, serum creatinine, urine routine examination, 24-hour urinary protein or spot UPCR, and renal biopsy findings) were noted. The following details of treatment received prior to enrolment were noted: use of intravenous pulse steroid before starting oral prednisolone, choice of induction immunosuppressive [cyclophosphamide (CYC) as per the Euro-Lupus Nephritis Trial regimen (ELNT-CYC), CYC as per the NIH protocol (NIH-CYC), mycophenolic acid (MPA), tacrolimus (Tac) or rituximab (RTX)], use of hydroxychloroquine and angiotensin-converting-enzyme (ACE) inhibitors.

Treatment protocol

Once RLN was considered, the treatment strategies employed included a switch to another first-line drug, for example, MPA if the patient had received CYC and vice versa. Alternative treatment options considered during a switch were tacrolimus, multitarget therapy (MPA+Tac), or RTX. This decision was based on the treating physician's discretion in consultation with the patient. Mycophenolate mofetil or enteric coated-MPA dose was 2g and 1.44g, respectively adjusted to the maximum tolerable dose. CYC was given monthly in the dose range of 500-1000 mg/m^2 (NIH-CYC). Tacrolimus was given in a dose of 0.025-0.1 mg/kg with the blood levels titrated between 4-10 ng/ml in those showing inadequate response. Rituximab was given as two 1g intravenous infusions 15 days apart. All patients received a maintenance dose (<0.15 mg/kg/d) of oral corticosteroids, hydroxychloroquine, calcium/vitamin D, and ACE inhibitors. During switching, no increase in oral steroid dose was done.

Following were recorded during a flare and every three months: Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), response to treatment, and adverse events. The institutional ethics committee approved this study (EC/NIMS/2209/2018). Written informed consent was obtained from all patients.

Statistical analysis

Baseline characteristics of patients were presented as mean (SD) or median (IQR) for continuous variables and percentages for categorical variables as appropriate. Comparisons among CR, PR, and NR

groups were made using ANOVA and chi-square tests. Predictors of renal outcome were assessed using Cox regression analysis. Statistical analysis was carried out with SPSS software (version 21). P-value < 0.05 was considered to represent a statistically significant difference.

Results

Out of 48 patients enrolled for the study, 12 were those who had no response by three months, 29 had not achieved PR at six months, and seven had not attained CR after two years of starting induction treatment. Two patients were lost to follow-up after six months, and one died within two months of enrolment. Forty-five patients completed nine months of follow-up and were considered for further analysis. The baseline disease characteristics are summarized in Table 1.

Renal biopsy was available in 43 patients (Table 2). Five patients either refused consent or had inadequate tissue yield. The first biopsy was done at the onset of lupus nephritis in 26 and after induction therapy failure in 17. In 8 patients, a repeat renal biopsy was available. The mean interval between biopsies was 2 (±1) years. A histological class transformation was seen in 6 patients (Table 3). In 3 patients, the renal biopsy was repeated for the third time. Renal biopsy could not be performed in the rest of the patients due to contraindications (thrombocytopenia, ascites, anasarca, orthopnoea, active infection) or unwillingness for the procedure. They were not different from those who were biopsied in terms of urinary and serological abnormalities.

All the patients included in the study were refractory to one or more or combinations of IS agents. The average number of IS agents used in each patient in the past was 3 (±1). At the time of enrollment, the disease was refractory to CYC in 38 patients (NIH-CYC in 33 and ELNT-CYC in 5); MPA in 17; Tac, RTX, and MPA+Tac in one patient each. After enrollment, IS agent(s) choice was guided by prior IS used, the severity of nephritis, involvement of other organ systems, comorbid conditions, and purchasing capacity of the patient. Thus MPA was used as the next IS agent in 20, MPA+Tac in 9, NIH-CYC in 8, tacrolimus in 3, rituximab as monotherapy in 1, and combination with tacrolimus and MPA in 2 patients each. In 18 patients, a second switch (MPA+Tac in 9, rituximab as monotherapy in 3 and combination with MPA in 2, tacrolimus alone in 2, NIH-CYC and MPA in 1 patient each) was needed due to persistent refractoriness to treatment. Six patients required a third switch (MPA+Tac in 2, RTX+MPA in 2 and, RTX monotherapy, CYC+Tac, CYC-NIH in one each). One further non-responder was switched to a combination of MPA+Tac. The most common sequence of switch among IS agents was CYC to MPA in 13 patients (Figure 1) and there was no significant difference in treatment outcome based on the sequence of IS followed.

At the end of a median follow-up of 15 (12-27) months, 28 of 45 had a CR, 9 had a PR, and 8 showed no response to therapy. Univariate analysis of the following factors: age, sex, duration of disease, nephritis, number of organ systems involved, baseline SLEDAI, leukopenia, hypertension, presence of anti-dsDNA, low C3 and or C4, serum albumin, 24-hour proteinuria, spot UPCR, biopsy class or IS therapy revealed that none predicted renal response. There was no significant difference in treatment outcome among

individual IS agents (Figure 2, Table 4). No patient had either doubling of baseline creatinine or ESRD. There were three deaths.

Four patients had severe adverse effects. One patient developed tubercular monoarthritis of the right knee at 12 months. Another developed CYC induced severe leukopenia (TLC=500/mm^3). The same patient later developed an epidural abscess and succumbed to sepsis with multi-organ dysfunction. Two other deaths due to sepsis occurred, one within three months of starting RTX and another in a non-responder to RTX and MPA. None of these patients had rising creatinine or ESRD before death.

Discussion

This study shows that in refractory lupus nephritis (defined, as suggested by the EULAR/EDTA group), a change in immunosuppressive agent leads to an overall response (CR+PR) in four-fifth of the patients. The combination of tacrolimus and mycophenolate appears to be most effective in producing a response. Renal failure is rare during short-term follow-up and death is related to infection.

In our study, a combination of MPA and tacrolimus, also termed multitarget therapy (MTT), produced a high global response rate. Response rates (complete and partial) ranging from 57-95% have been reported in previous studies (RCT [15] or observational studies [16-18]) which included 64 patients receiving this combination.

The response to MPA as a single agent in almost half the patients in our study was much lower than the 87% response seen in Hispanic patients with relapsing or refractory LN [19]. While their population had a higher incidence of proliferative nephritis, it did include patients with relapsed disease which may explain the lower response rate in our study. However racial differences in treatment response to MPA have also been suggested in literature [20].

With NIH-CYC, half the patients had CR. One patient who was refractory to multiple IS agents, including RTX had a complete response on receiving a combination of NIH-CYC and tacrolimus. While EULAR/EDTA recommends either MPA or CYC as first-line therapy in LN and a switch to either agent if the first fails, there is no data available on cyclophosphamide as the next remission inducing agent, if the primary regimen fails [12].

In the present study, regimes that included rituximab produced a response rate of 54%. Many studies which have used RTX, alone or in combination, in RLN have been included in a systematic review [21] and a meta-analysis [22], reporting global response rates of 74% and 70-78%, respectively. There have been limiting factors with these studies that include marked heterogeneity in the definition of refractoriness to therapy and variation in the RTX doses and regimens used.

Tacrolimus as monotherapy showed no response in any of our patients at a mean dose of 4 mg at the last follow-up. Two studies on tacrolimus in 35 LN patients not responding to sufficient

cyclophosphamide report very high response rates [23,24]. These differences may be explained by the rapid escalation of dose on follow-up in those studies.

Within the median duration of follow-up of 15 months, no patient in our study had a doubling of serum creatinine or progression to ESRD. Deaths in RLN patients are often due to infection [25] but may also be due to disease activity [19]. All deaths in our study followed severe infection.

In a small subset where repeat renal biopsies were available, frequent class transformation was noted. There was accrual of membranous lupus nephritis in four patients. The consequent proteinuria, leading to these patients being classified as refractory lupus nephritis. In studies reporting repeat renal biopsies in patients with ongoing or relapsed LN, it is shown that patients with proliferative LN continue to show the same findings with a transformation from class 3 to 4, while those with non-proliferative LN (Class 2 or Class 5) may accrue proliferative changes [26,27]. Though our sample size is not representative, switching from membranous to proliferative LN was not noted in our study.

The present study is, to our knowledge, the first prospective study from India and among the largest reported in the literature assessing treatment outcomes in patients of RLN in a real-world scenario over one year. Numerically best responses were seen using MPA and tacrolimus combination while switching IS agents in any sequence proved effective in almost half the patients. Limitations of sample size and problems in using randomization in this situation will continue to thwart efforts to understand the best way forward in patients with refractory lupus nephritis.

Conclusion

In the present study on patients with lupus nephritis who worsened within three months of induction therapy or did not achieve at least a partial response at six months or complete response at 24 months, slightly less than two-thirds of the patients responded to a change in immunosuppression while a significant minority still showed no response to therapy. During the follow-up period of more than a year, none of these patients had a worsening renal function. However, three deaths were noted, all in the rituximab recipients, mainly due to infection.

List Of Abbreviations

ACE	Angiotensin-converting-enzyme
ACR	American College of Rheumatology
AI	Activity index
ANOVA	Analysis of variance
CI	Chronicity index
CR	Complete renal response
CYC	Cyclophosphamide
ELNT-CYC	Euro-Lupus Nephritis Trial regimen of cyclophosphamide
ESRD	End-stage renal disease
EULAR/EDTA	European League Against Rheumatism and European Renal Association/European Dialysis and Transplant Association
GFR	Glomerular filtration rate
IQR	Interquartile range
IS agent	Immunosuppressive agent
ISN/RPS	International Society of Nephrology/Renal Pathology Society
LN	Lupus nephritis
MPA	Mycophenolic acid
MTT	Multitarget therapy
NIH	National Institute of Health
NR	No renal response
PR	Partial renal response
RLN	Refractory lupus nephritis
RTX	Rituximab
SD	Standard deviation
SLE	Systemic lupus erythematosus
SLEDAI	Systemic lupus erythematosus disease activity index
SLICC	Systemic lupus international collaborating clinic criteria
Tac	Tacrolimus
UPCR	Urine protein/creatinine ratio

Declarations

Ethics approval and consent to participate: The institutional ethics committee approved this study (EC/NIMS/2209/2018). Written informed consent was obtained from all patients.

Consent for publication: Not applicable

Availability of data and material: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

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Authors' contributions: SG, PKD and LR analyzed and interpreted the patient data and were major contributors in writing the manuscript. MU performed the renal histological examination. All authors read and approved the final manuscript.

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Tables

Table 1
Baseline characteristics of RLN Patients

Patient variables (n)	**n = 45**
Age, years [mean (SD)]	27 (8)
Females [n]	37
Duration of SLE, years [median (IQR)]	3 (2–6)
Duration of refractoriness of nephritis, months [median (IQR)]	6 (6–11)
Baseline SLEDAI [mean (SD)]	12 (4)
24 hour proteinuria, gram [median (IQR)]	2.0 (1.4–4.8)
Spot UPCR [median (IQR)]	3.1 (1.8–4.4)
Active urinary sediments (Haematuria/Pyuria) [n]	32 (20/29)
Hypertension [n]	14
S. Creatinine [mean (SD)]	0.7 (0.3)
S. Albumin [mean (SD)]	2.9 (0.6)
Low complements (C3 and or C4) [n]	34
High dsDNA (above lab cutoff) [n]	34

Table 2

Renal biopsy findings from 43 patients

Renal biopsy done at the onset of LN	**26**
Proliferative LN/Class III/IV (n)	**16**
Membranous LN/Class V (n)	**4**
Mixed LN/Class III/IV + V (n)	**5**
Mesangial proliferative/Class II (n)	**1**
Renal biopsy done at the onset of RLN	**17**
Proliferative LN/Class III/IV (n)	**9**
Membranous LN/Class V (n)	**5**
Mixed LN/Class III/IV + V (n)	**3**
AI [mean (SD)]	8 (3)
CI [mean (SD)]	0

Table 3

Histological class transformation in 8 patients with serial renal biopsies available.

S. No.	First renal biopsy (A)	Second renal biopsy (B)	Third renal biopsy (C)	Interval between A and B (years)	Interval between B and C (years)	Class switch
1	III	IV	IV	1	5	Yes
2	V	V	V	4	3	No
3	II	IV + V	IV	2	4	Yes
4	V	V	-	1	-	No
5	III	III + V	-	2	-	Yes
6	III	IV	-	2	-	Yes
7	IV	IV + V	-	2	-	Yes
8	IV	V	-	1	-	Yes

Table 4

Treatment outcomes grouped by type of immunosuppression used

S. No.	Immunosuppressive agent	No. of patients	Outcome	Time to response (months)
1.	MPA + Tac	21	No Response: 7 Response: 14	6 (3–9)
2.	MPA	21	No Response: 11 Response: 10	9 (3–9)
3.	CYC-NIH	10	No Response:5 Response: 5	9 (6–9)
4.	RTX	5	No Response:2 Response: 3	6 (3–9)
5.	RTX + MPA	6	No Response:3 Response: 3	3 (3–9)
6.	RTX + Tac	2	No Response:1 Response: 1	3
7.	Tacrolimus	5	No Response: 5	-
8.	CYC + Tac	1	Response: 1	3

Figures

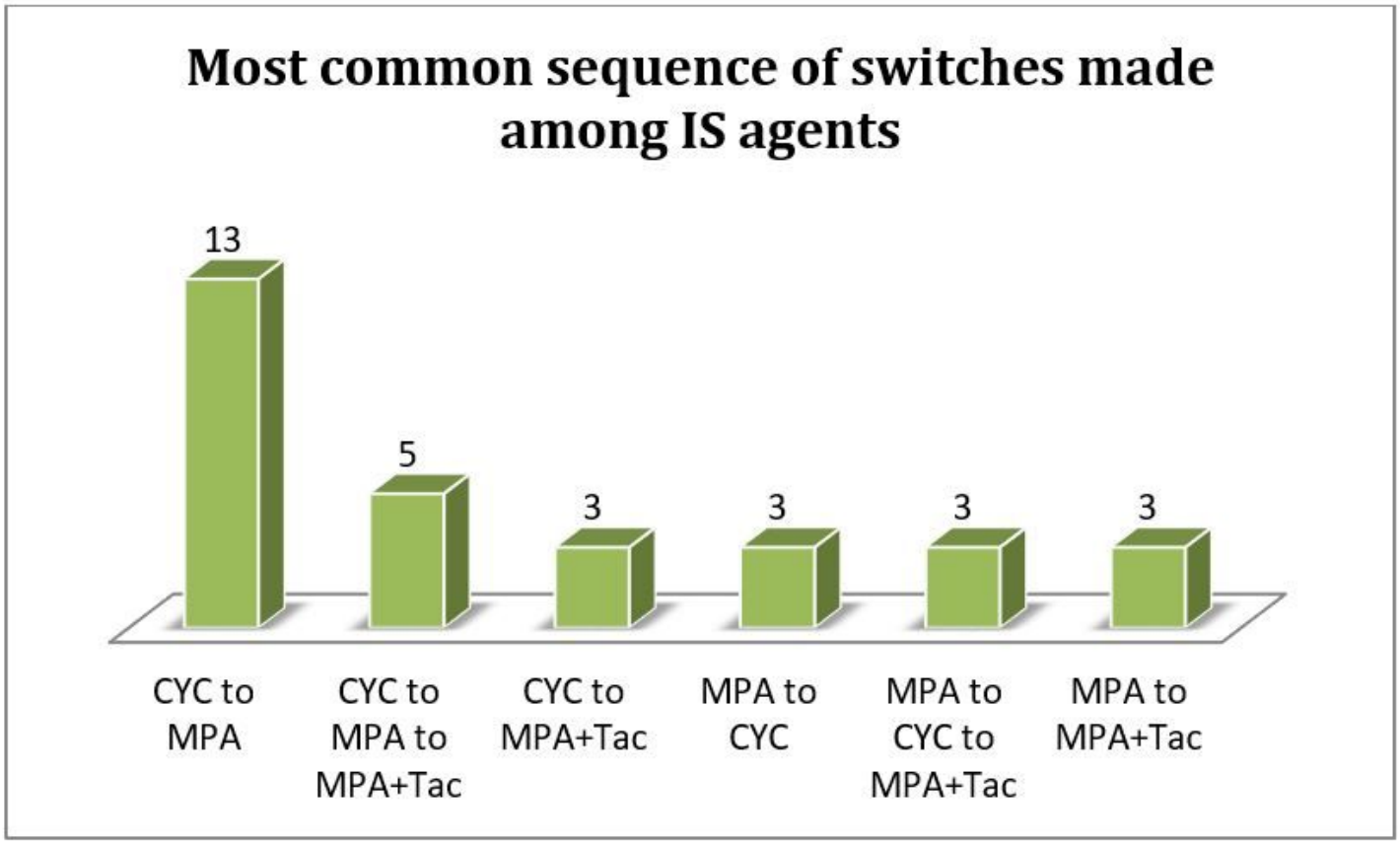

Figure 1

Most common sequence of switches made among IS agents

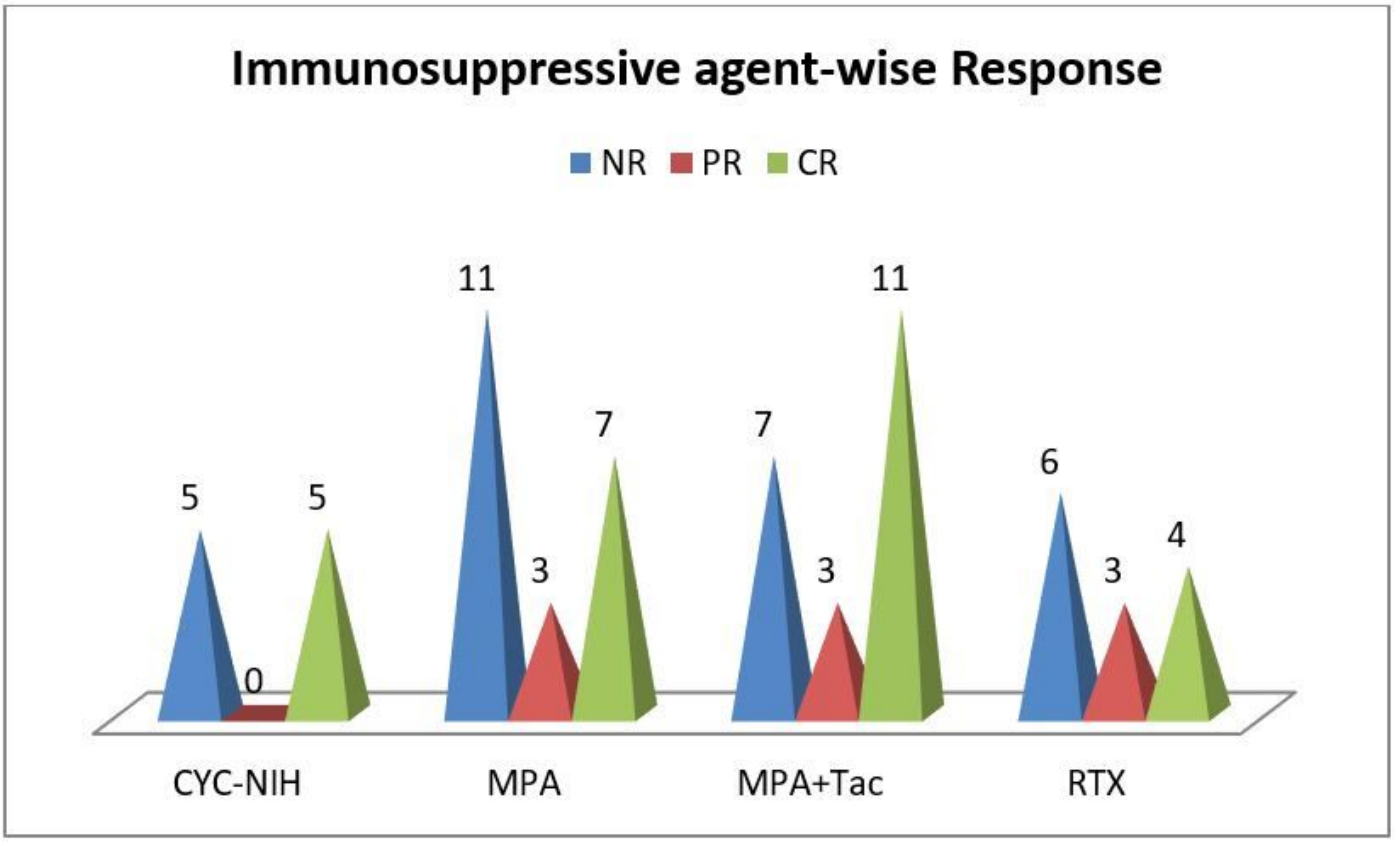

Figure 2

Treatment outcomes with individual IS agents