

Glucocorticoids in Management of Adult Rheumatoid Arthritis-Current Prescribing Practices and Perceptions of Physicians in India: GLUMAR Survey

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Abstract

Background: Several questions about use of glucocorticoids in rheumatoid arthritis are unanswered.

Objective: Understanding perspectives of physicians regarding use of glucocorticoids in rheumatoid arthritis management.

Material and methods: Rheumatologists were interviewed to understand their perspectives and experiences on use of glucocorticoids in rheumatoid arthritis treatment.

Results: Of the enrolled 150 physicians, 74% reported using glucocorticoids "sometimes to always" in the initial treatment whereas 143 (95.4%) reported it using "sometimes to always" in acute exacerbations; 40% sometimes as an adjuvant to disease modifying antirheumatic drugs therapy. Oral low dose prednisolone or equivalent (<15 mg/day) is used by 101 (67.3%) physicians in up to 50% patients. Intra-articular low dose and high dose steroid injections are used by 98 (65.3%) and 55 (36.7%) physicians in up to 50% patients respectively. All physicians used oral methylprednisolone whereas prednisone, triamcinolone and hydrocortisone was used by 98.7%, 98.7% and 97.3% physicians respectively. For short term course, 92 (61.3%) physicians prescribe 5-10 mg/day of prednisone or equivalent. Clinical improvement is excellent and very good according to 36.7% and 44.0% physicians. Functional improvement is excellent and very good according to 26.7% and 38.7% respectively. Weight gain, puffiness of face, fluid retention, osteoporosis, hyperglycemia, hypertension, nausea, weakness, infection, cataract, sleep disturbances, psychosis and glaucoma were the adverse events reported by 121 (80.7%), 115 (76.7%), 100 (66.7%), 87 (58%), 81 (54%), 56 (37.3%), 51 (34.4%), 46 (30.7%), 44 (29.3%), 36 (24%), 29 (19.3%), 23 (15.3%) and 19 (12.7%) physicians in past six months respectively.

Conclusion: Steroids usage for the treatment of rheumatoid arthritis in adult patients is very common among rheumatologists in India. According to this physicians' opinion based survey, overall tolerability, safety and patient compliance with oral GCs is fair to excellent. Short term use is not a major concern from safety point of view.

Introduction

Rheumatoid arthritis (RA), an autoimmune disorder which affects about 0.5-1% people results in significant morbidity and mortality because of extra articular problems and associated comorbidities [1-3]. Similarly, articular mobility and disability is also a major concern in RA. Glucocorticoids (GCs) and Disease Modifying Anti-Rheumatic Drugs (DMARDs) are common medicines used in the management of RA.

Glucocorticoids (GCs) are one of the important, conventional and widely used agents because of their ability to decrease signs and symptoms in inflammatory disorders [4,5]. These drugs also exert disease-modifying effect, especially when used in the early stage of the disease [6,7] and may avoid development of severe consequences in patients with severe clinical presentation at the beginning [8]. Even after their presence for more than six decade and introduction of other therapies, GCs remain the cornerstone therapy for management of RA [2,6,9]. Despite wide experience, several questions about use of GCs still remain unanswered. According to recently published systematic

review of international guidelines and consensus statement, the recommendations for the use of GC need more robust evaluation of dose, timing and duration. Moreover, there are concerns about adverse events among both physicians and patients. The risk of adverse events has potential to adversely affect the adherence and thereby the compliance [4,10]. Indian data on physician's opinions regarding use of GCs in RA are limited.

Objective

To understand the perspectives of Indian physicians regarding the use of GCs and to determine the prescribing pattern of GCs and other agents in RA management.

Keywords: Rheumatoid arthritis; Autoimmune disorder; Anti-rheumatic drugs; Glucocorticoids; Gastric symptoms

Abbreviations: RA: Rheumatoid Arthritis; GCs: Glucocorticoids; DMARDs: Disease Modifying Anti-Rheumatic Drugs.

Material and Methods

In this survey rheumatologists or physicians treating patients with rheumatoid arthritis were contacted telephonically for their willingness to participate in the survey. The designated personnel travelled to the physicians' clinic/hospital for taking an interview of the willing physicians. Interviews were conducted in accordance with the pre-designed paper-based questionnaire which involved questions on the perspectives and experiences of physicians on various aspects of RA treatment with GCs and DMARDs, other treatment regimens, types, doses, duration of treatment and adverse events with oral GCs.

Physician responses for clinical and functional improvement, delay in radiological progression, tolerability, patient compliance and satisfaction with oral GC for RA were assessed on a 5-point Likert scale (excellent, very good, good, fair and poor). Different factors affecting physicians' decision while selecting, adding or modifying treatment regimen for the RA patients were also recorded. The survey was conducted between the period of July to November 2016.

Statistical Analysis

All statistical analyses were conducted using SAS system, version 9.4. Summary of categorical data is presented as numbers and

percentages. Missing category is presented, in case of non-availability of the data.

Results

A total of 150 Rheumatologist from India were enrolled in this survey of which 66% were from private hospitals and 28% from private clinics. A total of 111 (74%) physicians reported using GC "sometimes to always" in the initial treatment of RA whereas 143 (95.4%) reported it using "sometimes to always" in the treatment of acute exacerbations of RA. Eighty two (54.7%) physicians use GCs "very often to always" to ease symptoms while DMARDs start to take effect. Ninety eight (65.3%) physicians "rarely or never" use GCs for maintenance treatment whereas 69 (46%) use it "very often to always" for symptom control when no other treatment option is feasible. Forty percent physicians sometimes use GCs as an adjuvant to DMARD therapy (Table 1).

	Initial treatment	Acute exacerbations/ flare up	To ease symptoms while DMARDs start to take effect	For maintenance (long term)	symptom control when no other treatment option is feasible	Adjunct to DMARD therapy
Always	32 (21.3%)	51 (34.0%)	25 (16.7%)	3 (2.00%)	25 (16.7%)	12 (8.00%)
Veryoften	40 (26.7%)	70 (46.7%)	57 (38.0%)	14 (9.3%)	44 (29.3%)	27 (18.0%)
Sometims	39 (26.0%)	22 (14.7%)	53 (35.3%)	35 (23.3%)	50 (33.3%)	60 (40.0%)
Rarely	25 (16.7%)	4 (2.67%)	12 (8.00%)	53 (35.3%)	21 (14.0%)	39 (26.0%)
Never	14 (9.3%)	3 (2.00%)	3 (2.00%)	45 (30.0%)	10 (6.67%)	12 (8.00%)

Table 1: Use of GCs in RA.

Different regimens and routes of administrations of GCs used by physicians are presented in Table 2.

Oral low dose prednisolone (<15 mg/day) is used by 101 (67.3%) physicians in up to 50% of cases whereas 109 (72.7%) physicians use it on alternate day. Initial high dose oral prednisone (60 mg/day) is tapered by 87 (58%) in up to 50% patients. Seventy six (50.7%)

physicians use low dose intramuscular steroid injections in up to 50% patients whereas 51 (33.9%) use high dose in up to 50% patients. Intra-articular low dose and high dose steroid injections are used by 98 (65.3%) and 55 (36.7%) physicians in up to 50% patients respectively (Table 2).

	Oral GC- Low dose equivalent to prednisolone <15 mg/day daily	Oral GC- Low dose equivalent to prednisolone <15 mg/day on alternate days	Oral GC-High dose equivalent to prednisone started at 60 mg/day followed by tapering	Intramuscular steroid injections- low dose	Intramuscular steroid injections- high dose	Intra-articular steroid injections-low dose	Intra-articular steroid injections-high dose
None	10 (6.7%)	37 (24.7%)	61 (40.7%)	59 (39.3%)	89 (59.3%)	50 (33.3%)	91 (60.7%)
<10%	44 (29.3%)	56 (37.3%)	45 (30.0%)	37 (24.7%)	35 (23.3%)	47 (31.3%)	41 (27.3%)
10-25%	29 (19.3%)	34 (22.7%)	25 (16.7%)	25 (16.7%)	8 (5.33%)	38 (25.3%)	10 (6.67%)
26-50%	28 (18.7%)	19 (12.7%)	17 (11.3%)	14 (9.33%)	8 (5.33%)	13 (8.67%)	4 (2.67%)
51-75%	26 (17.3%)	2 (1.33%)	2 (1.33%)	9 (6.00%)	2 (1.33%)	2 (1.33%)	3 (2.00%)

>75%	13 (8.7%)	1 (0.67%)	0 (0.0%)	6 (4.00%)	7 (4.67%)	0 (0.0%)	1 (0.67%)
Missing	-	1 (0.67%)	-	-	1 (0.67%)	-	-
Total	150 (100%)	150 (100%)	150 (100%)	150 (100%)	150 (100%)	150 (100%)	150 (100%)

Table 2: Different regimens and routes of administration of GC use.

All physicians participated in survey use oral methylprednisolone. Percentages of physicians using prednisolone, triamcinolone and hydrocortisone are shown in Figure 1. Other oral GCs are used by 25.3% physicians of which 71.7% prefer deflazacort.

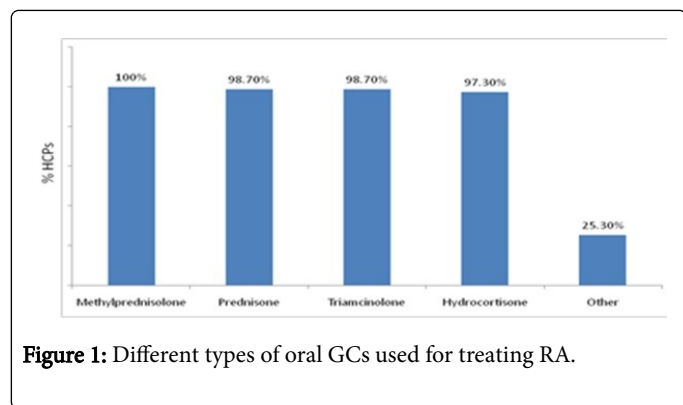


Figure 1: Different types of oral GCs used for treating RA.

For the short term course, 92 (61.3%) physician prescribe 5-10 mg/day of prednisone or equivalent while 24 (16%) prescribe less than 5 mg/day. A total of 22 (14.7%) and 12 (8%) prescribe 10-15 mg/day and more than 15 mg/day prednisone respectively.

A total of 53 (35.3%) physicians prefer to use only short course (i.e. 5-10 days) of oral GCs. A total of 45 (30%), 50 (33.3%) and 2 (1.3%) use prednisone less than 5 mg/day, 5-10 mg/day and 10-15 mg/day respectively. Of those who use less than 5 mg per day, 37 (82.2%) use it up to three months. Similarly, of those who use 5-10 mg prednisone per day, 45 (90%) use it up to six months. Fifty percent of physicians who use prednisone 10-15 mg/day use it up to three months and 6-12 months respectively (Table 3).

Parameter	N (%)
Prefer only short courses for 5 to 10 days	53 (35.3%)
10 days to 1 month	Nil
<5 mg/day of prednisone (or equivalent)	45 (30.0%)
1 to 3 months	37 (82.2%)
3 to 6 months	7 (15.6%)
>12 months	1 (2.22%)
5 to 10 mg/day of prednisone (or equivalent)	50 (33.3%)
1 to 3 months	16 (32.0%)
3 to 6 months	29 (58.0%)
>12 months	5 (10.0%)
10 to 15 mg/day of prednisone (or equivalent)	2 (1.3%)
1 to 3 months	1 (50.0%)
3 to 6 months	Nil
6 to 12 months	1 (50.0%)

Table 3: Routine average oral dose of oral GCs for treatment of RA.

Clinical improvement i.e. reduction in number of tender/swollen joints was reported to be “excellent” by 36.7% of the physicians and “very good” by 44.0% physicians. Functional improvement (better quality of life) with GCs reported as “excellent and very good” by 26.7% and 38.7% physicians respectively. Delay in radiological progression after using GCs for treating RA was reported to be “good and fair” by 32% and 34.7% physicians respectively. Tolerability of GCs was reported as “good to excellent” by 134 (89.3%) physicians when

given as short term course as opposed to 77 (51.4%) when used as long term (>3 months). Compliance with GCs, when given as short term course was rated to be “very good” by 40.0% physicians as compared to that with long term course which was rated “fair” by 38.0%. Patient satisfaction for a short term course was reported to be “very good” by 46.7% of the physicians. The percentages of physicians reporting patient satisfaction with long term GCs as “very good”, “good” and “fair” were same i.e. 28.7% each (Table 4).

	Clinical improvement	Functional improvement	Delay in radiological progression	Tolerability when given as short-term course (<3 months)	Tolerability when given for more than 3 months	Compliance when given as short-term course (<3 months)	Compliance when given for more than 3 months	Patient satisfaction when given as short-term course (<3 months)	Patient satisfaction when given for more than 3 months
Excellent	55 (36.7%)	40 (26.7%)	13 (8.67%)	29 (19.3%)	7 (4.67%)	34 (22.7%)	6 (4.00%)	33 (22.0%)	6 (4.00%)
Very Good	66 (44.0%)	58 (38.7%)	31 (20.7%)	58 (38.7%)	21 (14.0%)	60 (40.0%)	28 (18.7%)	70 (46.7%)	43 (28.7%)
Good	27 (18.0%)	38 (25.3%)	48 (32.0%)	47 (31.3%)	49 (32.7%)	43 (28.7%)	45 (30.0%)	40 (26.7%)	43 (28.7%)
Fair	2 (1.33%)	14 (9.33%)	52 (34.7%)	13 (8.67%)	62 (41.3%)	12 (8.00%)	57 (38.0%)	7 (4.67%)	43 (28.7%)
Poor	0 (0.0%)	0 (0.0%)	6 (4.00%)	3 (2.00%)	11 (7.33%)	1 (0.67%)	14 (9.33%)	0 (0.0%)	15 (10.0%)

Table 4: Effectiveness, tolerability, patient compliance and satisfaction of GCs in RA.

A total of 34.7% physicians did not report tapering of oral GC dose as they use them only for short term. Out of those physicians who prefer long term doses, 38.7% start tapering the dose after one to three months and 16.7% physicians taper the dose after two weeks. A total of 120 (80%) physicians use supplements after 3-6 months of steroid use whereas 23 (15.3%), 6 (4%) and 1 (0.67%) prescribe it after six to 12 months, 12-18 months or more than 18 months of treatment to prevent or stop steroid-induced osteoporosis. Calcium, vitamin D, bisphosphonates and calcitonin is preferred by 92%, 98.7%, 63.3% and 20% physicians respectively. Remaining 8.6% physicians prefer other supplements.

Weight gain, puffiness of face, fluid retention, osteoporosis, hyperglycemia, hypertension, nausea, weakness, infection, cataract, sleep disturbances, psychosis and glaucoma were the adverse events reported by 121 (80.7%), 115 (76.7%), 100 (66.7%), 87 (58%), 81 (54%), 56 (37.3%), 51 (34.4%), 46 (30.7%), 44 (29.3%), 36 (24%), 29 (19.3%), 23 (15.3%) and 19 (12.7%) physicians in past six months respectively

A total of 84 (56%) of the physicians mentioned that $\geq 76\%$ patients do not take steroids on empty stomach whereas 106 (70.7%) of the physicians reported that $\geq 51\%$ patients need or take antacids to relieve gastric symptoms. One hundred four (69.3%) physicians mentioned that $\geq 51\%$ patients take steroids in the morning whereas 72 (46.7%) physicians mentioned that $\leq 50\%$ patients report adverse events immediately. According to 121 (80.7%) physicians up to 50% patients stop GCs without consulting.

Clinical judgement, laboratory assessment, clinical outcome measures, radiographical imaging/ultrasound, age/gender/general health of the patients are the parameters considered while deciding treatment plan for RA according to 98%, 97.3%, 68%, 56.7% and 55.3% physicians respectively (Figure 2).

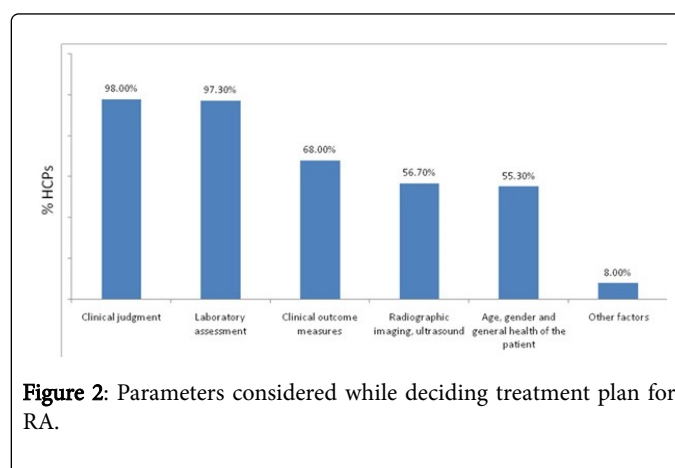


Figure 2: Parameters considered while deciding treatment plan for RA.

Majority of physicians (92.7%) consider painful and swollen joints and number of joints (86.0%) involved while selecting DMARDs for the treatment of RA whereas 70.7%, 72% and 72.7% physicians consider pain intensity, disease activity score 28/DAS 28 and physical functioning and mobility respectively. Patient's general health is considered by 66.0% physicians while rheumatologists' impression of overall disease activity and patient's level of comfort in expressing concerns were considered by 46.0% and 29.3% physicians.

While considering intrarticular steroid, involvement of knee joint, temporomandibular joint, number of joints involved, rapid relief pain, range of movement, morning stiffness, tight control treatment strategies to quickly minimize inflammation and disease progression, lesser side effects than systemic steroids are the parameters according to 115 (76.7%), 30 (20%), 36 (24%), 105 (70%), 75 (50%), 39 (26%), 56 (37.3%) and 51 (34.0%) respectively.

Majority of physicians consider worsening of disease as per clinical and/or radiographic assessment (94.0%) and increase in painful and swollen joints affecting functioning and mobility (93.3%) followed increase in DAS 28 (80.7%). Other parameters considered include presence of risk factors for severe RA (62.0%), patient's general health (58.7%) and patient's dissatisfaction with current DMARDs (53.3%). Patient's willingness to change DMARDs (32.0%) and patient's level of comfort in expressing concerns (31.3%) were also considered by some physicians. Majority of physicians (94.0%) considered time frame of

less than six months for defining early RA in patients while six percent consider the time frame of less than 12 months.

For early RA patients, majority of physicians prefer step-up combination therapy with DMARDs (70.7%), followed by initial combination therapy with a DMARD and low dose oral corticosteroid (54.7%), sequential monotherapy with DMARDs (53.3%), and analgesics and NSAIDs (42.7%). Thirty percent of physicians each prefer intensive therapy with intra-articular or intra-muscular corticosteroids along with DMARDs and combination therapy in early RA (COBRA) -step-down combination regimen of high dose corticosteroid and DMARDs (prednisolone, methotrexate, and sulfasalazine). Initial combination with synthetic DMARD and a biological DMARD was reported by 18.0% of physicians. For established RA patients, step-up combination therapy with DMARDs and initial combination therapy with a DMARD with low dose oral corticosteroid were preferred by 64.0% and 62.7% physicians respectively followed by 46.0% physicians who preferred combination therapy in early RA (COBRA)-step-down combination regimen of high dose corticosteroid and DMARDs (prednisolone, methotrexate, and sulfasalazine). Intensive therapy with intra-articular or intra-muscular corticosteroids along with DMARDs was preferred by 38.7% physician while sequential monotherapy with DMARDs was preferred by 35.3% physician. Thirty percent physician preferred initial combination with synthetic DMARD and biological DMARD, and 22.2% physician preferred analgesics and NSAIDs.

Discussion

Glucocorticoids play an important role in the management of RA [11,12]. Despite being in use since many decades, GCs are still cornerstone for the treatment of RA. In this study, we examined prescription pattern and opinions of physicians about GCs use in the treatment of RA.

As documented in literature [2,4,13,14], GCs are widely used and are an important therapy for the management of RA in India. About three forth physicians use GC “sometimes to always” in the initial treatment of RA. Our observation is in accordance with the evidence of its common usage even after introduction of several other options for the management [4]. The percentage of physicians using GCs in acute exacerbation of disease is still more. This wide spread usage may be because of the ability to quickly reduce inflammation and thereby signs and symptoms [4]. GCs can be useful to tide over till DMARDs show their effect [13]. In accordance to this, close to 55% physicians reported using them “very often to always” for relieving symptoms before DMARDs show effect.

Long term use of GCs for maintenance therapy is a controversial [13]. Close to two third physicians “rarely or never” use them for maintenance treatment. Some use them if other treatment option is not available or contraindicated. If used with precautions, long term therapy of GCs can be a good choice considering its anti-inflammatory benefits and protective action against structural damage [13]. Glucocorticoids can be used as monotherapy [15] as well as in combination with other agents. Use of GCs as an adjuvant with DMARDs is also common among Indian physicians.

Low dose of steroids is one of the measures to minimize the risk of adverse events [13]. Present study also observed a large number of physicians using oral low dose prednisolone and many use it on alternate day. If used in high doses initially, physicians taper the dose later. Use of intramuscular and intra-articular steroid injection is also

common among Indian doctors. Oral methylprednisolone, prednisone, triamcinolone and hydrocortisone are the most commonly used. Of the newer therapies, deflazacort use is very common.

For the short term course, prednisone 5-10 mg or equivalent per day is preferred by large number of physicians and mostly up to six months. Prednisone 10-15 mg or equivalent per day up to 12 months is also common practice of many physicians. Two year adjunct treatment with 10 mg/day prednisone or equivalent has shown to increase the benefits of DMARD therapy [16].

Efficacy of GCs is well accepted [17]. Clinical and functional improvement was reported as excellent to very good by most while delay in radiological progression was reported as good to fair by almost two third physicians. Adverse effects especially with chronic use at higher dosages is a concern [17]. Tolerability was not a concern when used for short term, according to most physicians in this study. With long term, more physicians raised concerns. Compliance and satisfaction remains a problem among patients, according to many physicians. Dosage and duration of therapy and patient related factors determine the risk of adverse events with long-term usage [17]. A retrospective study from UK, showed that GC below 5 mg is not associated with elevated risk of mortality [18]. Similarly, short term use of moderate doses are also generally well tolerated [19].

In our study, some physicians who use GC for long term, reported tapering it after one to three months while few do it after two weeks. Low-dose can have acceptable safety even after long term use [20].

Osteoporosis is a concern with use of steroids [21,22]. The risk can be tackled by implementing anti-osteoporotic strategies [23]. An expert consensus statement from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) recommends assessment of patients for fracture risk. Bone preserving agents, calcium and vitamin D are useful for preventing GC related fractures [19]. Use of supplements was common and most physicians reported using supplements after 3-6 months of steroid use in our study. Cardiometabolic adverse are more common with longer duration of therapy and with higher doses [14,24-26]. In our study, some of these adverse events were reported by physicians. GCs should be used considering their benefit/risk ratio [11].

Important factors considered while selecting therapeutic agents include efficacy, safety and demographic parameters. Clinical condition and general health of the patient is one of the most important parameters while selecting DMARDs according to large number of physicians.

Intra-articular steroids are used in case of knee or temporomandibular joint involvement by some doctors. Number of joints involved, efficacy, onset of action, safety and impact on disease progression, are the other factors considered by physicians while selecting intraarticular steroid injection.

Worsening of disease is assessed based on the clinical and/or radiographic assessment by majority of physicians. Less than six months is early RA, according to most physicians.

Conventional synthetic DMARDs (as monotherapy or combination) are recommended in DMARD-naïve patients. Similarly, combination therapies with biological DMARDs are also used in the management of RA. Combination therapies of conventional synthetic with biological DMARDs are recommended in moderate to severe cases after failure of conventional synthetic DMARD treatment. Methotrexate is widely used agent in combination. If there is no contraindication,

methotrexate is the best choice for combination [27]. In our study, most physicians reported that for early RA patients, step-up combination therapy with DMARDs is the preferred approach whereas initial combination therapy with a DMARD and low dose oral GC is the second common approach. For established RA patients, step-up combination therapy with DMARDs and initial combination therapy with a DMARD with low dose oral corticosteroid are the two common approaches. Glucocorticoids are also widely used in combination with other disease-modifying anti-rheumatic drugs [26].

Overall, there was a high variability among physicians among treatment regimens, dosage, indications, duration of therapy as well as corticosteroid tapering time. Our study has some limitations. As this was an opinion based survey, the biases in the subjective responses can not be ruled out. There was no follow up of patients, hence the rates of reported adverse events should be carefully extrapolated. Convenience sampling is another limitation of the study. Nonetheless, the observations provide important insights about the management of RA in Indian patients especially with GCs. Examining differences of practice of using GCs for the management of RA in different centers could be interesting.

Conclusion

Use of steroids for the treatment of RA in adult patients is very common among rheumatologists. The most commonly used GCs were methylprednisolone, triamcinolone, prednisone, and hydrocortisone. According to this physicians's opinion based survey, overall tolerability, safety and patient compliance with oral GCs is fair to excellent. As per majority of physicians, upto 50% patients stop GCs without consulting. Adverse events does not seem to be a major concern with short term use. Overall tolerability, safety and patient compliance with oral GCs is fair to excellent.

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